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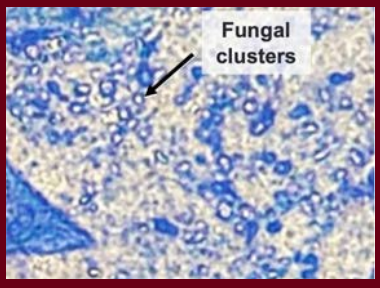

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy and Safety of Cosibelimab for Advanced Cutaneous Squamous Cell Carcinoma: An Expert Consensus Panel

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ABSTRACT

Background: Cutaneous squamous cell carcinoma (cSCC) represents a significant clinical challenge in patients with locally advanced (laCSCC) or metastatic (mCSCC) disease who are not candidates for surgery or radiation. In addition to PD-1 inhibitors, pembrolizumab and cemiplimab, cosibelimab, a PD-L1 inhibitor, has been recently approved by the US Food and Drug Administration (FDA) for laCSCC and mCSCC. Given its recent approval, practical guidance is needed to support clinician decision-making regarding cosibelimab's efficacy and safety.

Methods: A comprehensive literature review of PubMed and Google Scholar was completed for studies related to cosibelimab efficacy and safety in laCSCC and mCSCC. An expert panel of 9 dermatologists with significant expertise in the treatment of cSCC gathered to review the articles and create consensus statements on the role of cosibelimab in managing laCSCC and mCSCC. A modified Delphi process was used to approve each statement, and the strength of recommendation was assigned using the Strength of Recommendation Taxonomy (SORT) criteria.

Results: The literature search produced over 200 articles that met the criteria, and a screening of the studies for relevance resulted in 13 articles. The panel developed 6 consensus statements, with 5 unanimously adopted with a strength of "A".

Conclusion: Available data suggest that cosibelimab is an effective treatment for patients with laCSCC and mCSCC who are not candidates for surgery or radiation. Cosibelimab demonstrates a unique and favorable safety profile with no reported grade 4 or 5 immune-related adverse events after more than 2 years of follow-up.

J Drugs Dermatol. 2026;25(5):413-420. doi:10.36849/JDD.9954

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, with increasing incidence rates worldwide.[1] While most cases are successfully treated with surgical excision or radiation therapy, a subset of patients develop locally advanced cSCC (laCSCC) or metastatic cSCC (mCSCC) that is not amenable to standard treatments, presenting significant therapeutic challenges.[2,3]

cSCC features a high tumor mutational burden (TMB) and elevated prevalence in immunosuppressed individuals, indicating a circumvention of immune surveillance. The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint pathway plays a critical role in tumor immune evasion in cSCC. PD-1 is an inhibitory receptor primarily found on T cells that, when bound by its ligands, PD-L1 and PD-L2, found on antigen-presenting cells and many cancer cells, restrains T cells from full activation and proliferation, thereby suppressing antitumor responses. cSCC tumors exploit this pathway by overexpressing PD-L1 on tumor cells, which interacts with PD-1 receptors on T cells to promote T cell inhibition and immune evasion.[4] These characteristics make advanced cSCC an exceptionally prime candidate for immunotherapy.[2,5-10]

The treatment landscape for advanced cSCC has been transformed by the introduction of immune checkpoint inhibitors (ICIs). Cemiplimab (a fully human PD-1 monoclonal antibody) and pembrolizumab (a humanized PD-1 monoclonal

antibody) have received US Food and Drug Administration (FDA) approval for the treatment of laCSCC and mCSCC in patients who are not candidates for curative surgery or radiation. These PD-1-targeting therapies have led to significant improvements in advanced cSCC survival and quality of life.[11,12] However, treatment options are still limited for advanced cSCC patients, and side effects, including potentially life-threatening immune-related adverse events such as endocrinopathies, pneumonitis, colitis, hepatitis, and severe dermatologic reactions, can lead to discontinuation of treatment.[11-13]

Cosibelimab is a high-affinity, fully human monoclonal antibody targeting PD-L1 and is the most recently FDA-approved ICI for the treatment of laCSCC and mCSCC. While pivotal phase 1 studies have demonstrated its efficacy and safety in advanced cSCC, cosibelimab remains a newly approved therapy.[14,15] As such, expert evaluation of current clinical data is essential to guide optimal use in practice.

The purpose of this expert consensus panel was to review the published evidence on cosibelimab efficacy and safety in advanced cSCC and provide practical guidance to support clinicians as they integrate this newly approved therapy into the management of laCSCC and mCSCC.

MATERIALS AND METHODS

Literature Search and Study Selection

A targeted literature review of PubMed and Google Scholar was completed from October 1 to October 10, 2025, using keywords "cosibelimab," "CK-301," "cutaneous squamous cell carcinoma," "cSCC," "PD-L1 inhibitor," "pembrolizumab," "cemiplimab," "locally advanced," "metastatic," and "immune-related adverse events" along with Boolean term "AND" for English-language original research articles, systematic reviews, meta-analyses, and conference posters or presentations. Package inserts for cosibelimab, cemiplimab, and pembrolizumab were also reviewed. The literature was screened for relevance to the efficacy and safety of cosibelimab and comparative checkpoint inhibitors in advanced cSCC.

The 9 experts who participated in the panel were selected for their expertise in the management of advanced cSCC. The articles and presentations that met the inclusion criteria were distributed, and each member of the panel assigned levels of evidence based on the Strength of Recommendation Taxonomy (SORT) criteria.[16] These levels included level 1 (good-quality patient-oriented evidence), level 2 (limited-quality patient-oriented evidence), or level 3 (other evidence such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[16]

TABLE 1.

Strength of Recommendation Taxonomy (SORT) Criteria Level of Evidence for References Used in Modified Delphi Process

Reference	Citation	Study Title	Level of Evidence	Consensus
1	Clingan (2023)[15]	Efficacy and Safety of Cosibelimab, an Anti-PD-L1 Antibody, in Metastatic cSCC	1	(9/9)
2	Gorelik (2017)[18]	Poster: Preclinical Characterization of a Novel Full Human IgG1 Anti-PD-L1 mAb CK-301	3	(9/9)
3	Hughes (2021)[12]	Pembrolizumab for Locally Advanced and Recurrent/Metastatic cSCC (KEYNOTE-629 Study): an Open-Label Nonrandomized, Multicenter, Phase II Trial	1	(9/9)
4	Idris (2025)[19]	PD-L1 Inhibitor Cosibelimab for cSCC: Comprehensive Evaluation of Efficacy, Mechanism, and Clinical Trial Insights	2	(9/9)
5	Lin (2021)[20]	Poster: Semi-mechanistic PK/Target-Occupancy Modeling to Support Dose Justification for Anti–PD-L1 Clinical Candidate CK-301 (cosibelimab)	3	(8/9)
6	Migden (2018)[11]	PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma	1	(9/9)
7	Muñoz-Couselo (2024)[21]	Poster: Cosibelimab in Advanced cSCC: Long-Term Efficacy and Safety Results from Pivotal Study	1	(9/9)
8	Muñoz-Couselo (2024)[22]	Poster: Pembrolizumab for Locally Advanced or Recurrent/Metastatic cSCC: Long-Term Results of the Phase 2 KEYNOTE-629 Study	1	(9/9)
9	Plock (2023)[23]	Poster: PD-L1 Inhibitor Cosibelimab: Poppk Supports Comparability of 800 Mg Q2W and 1200 Mg Q3W Dosing Regimens Based on Recent FDA Criteria	3	(9/9)
10	Rischin (2025)[13]	Adjuvant Cemiplimab or Placebo in High-Risk cSCC	1	(9/9)
11	Ruiz (2025)[14]	Efficacy and Safety of Cosibelimab in Advanced cSCC: Results From a Pivotal Open-Label Study With a Median Follow-up of ≥2 Years	1	(9/9)
12	Spagnuolo (2018)[24]	"Comparison of the Toxicity Profile of PD-1 versus PD-L1 Inhibitors in Non-Small Cell Lung Cancer": Is There a Substantial Difference or Not?	3	(9/9)
13	Wang (2019)[25]	Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-Analysis	2	(8/9)

Abbreviations: cSCC, cutaneous squamous cell carcinoma; IgG, Immunoglobulin G; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks

Development of Consensus Statements

The panel convened on October 22, 2025, to discuss the studies and create consensus statements on cosibelimab efficacy and safety in advanced cSCC. A modified Delphi process, a standard method for developing dermatology recommendations, was used and required a supermajority of six of nine votes for adoption through iterative real-time voting.[17] Consensus statements were assigned a strength of recommendation of A (consistent, good-quality evidence), B (inconsistent or limited-quality evidence), or C (consensus, opinion, or disease-oriented evidence).[16]

RESULTS

Literature Search and Study Selection

The literature search resulted in over 200 articles that met the search criteria. After a comprehensive screening process, 13 references were selected. Studies were included if they reported efficacy and/or safety outcomes for cosibelimab in cSCC or informed comparative safety and/or efficacy of PD-1/PD-L1 inhibitors in advanced cSCC.

Levels of Evidence Designation

For the 13 references that were evaluated, the panel assigned level 1 evidence to 7 references, level 2 evidence to 2 references, and level 3 evidence to 4 references. Although several references initially received mixed evidence ratings, subsequent roundtable discussions allowed the panel to review and clarify the data, resulting in a supermajority consensus for all literature provided (Table 1).

The panel developed 6 consensus statements regarding the efficacy and safety of cosibelimab in advanced cSCC. Five statements were approved unanimously (9/9); one received supermajority support (7/9) (Table 2).

DISCUSSION

Statement 1: *Available evidence indicates that cosibelimab is an effective treatment for mCSCC and laCSCC. (SORT Level A)*

Pivotal clinical trials have evaluated cosibelimab for the treatment of laCSCC and mCSCC, generating the current evidence for its clinical activity. In the pivotal multicenter, multi-cohort, non-randomized phase 1 trial of 78 patients with mCSCC treated with cosibelimab 800 mg IV every 2 weeks, the objective response rate (ORR) was 47.4%, including 7.7% complete responses (CRs) and 39.7% partial responses (PRs) (Table 3). With a median follow-up of 29.3 months, the median duration of response (DOR) was not reached, with a range of 1.4+ to 45.3+ months. Among responders, 85% had an observed DOR ≥6 months, and 67% had an observed DOR ≥12 months.[15]

Extended follow-up (≥2 years; median 24-29 months) in 192 patients with mCSCC and laCSCC showed sustained activity, with ORRs of 50.0% and 54.8%, CRs of 12.8% and 25.8%, and PRs of 37.2% and 29.0%, respectively. In the mCSCC cohort, the estimated 24-month DOR rate was 72.1%. In the laCSCC cohort (median follow-up, 24.1 months), median DOR was not reached (8.3-31.3+ months). Among responders, 100% had an observed DOR of ≥6 months and 88% had an observed DOR of ≥12 months, with an estimated 24-month DOR rate of 80.2%.[14]

Interpretation of these efficacy findings requires consideration of several important limitations. Although the available data demonstrated clear efficacy signals, the evaluable evidence would be strengthened by longer follow-up durations and larger patient cohorts to fully characterize cosibelimab's long-term efficacy and safety profile. Additionally, and more fundamentally, the classification of cSCC as "locally advanced" lacks standardization, creating inherent challenges in translating

TABLE 2.

Consensus statements Consensus Statements and Corresponding Strength of Recommendations ***(consensus defined as ≥6 of 9 panelists; five statements approved unanimously [9/9] and one statement approved by supermajority [7/9]).***

Reference	Citation	Study Title
Available evidence indicates that cosibelimab is an effective treatment for metastatic and locally advanced cutaneous squamous cell carcinoma.	A	9/9
The efficacy of the PD-L1 inhibitor, cosibelimab, in cSCC is comparable to that of PD-1 inhibitors in similar patient populations.	A	9/9
Cosibelimab has a comparable safety profile and is characterized by lower level of high-grade adverse events compared to PD-1 inhibitors based on available data.	A	9/9
Given the current evidence, the absence of grade 4 and 5 immune-related adverse events with cosibelimab is clinically meaningful.	A	9/9
Given its favorable adverse event profile, cosibelimab may provide a clinical advantage compared to other systemic therapies for mcSCC and lacSCC.	A	9/9
The reduced risk for grade 4 and 5 adverse events with cosibelimab for the management of mcSCC and lacSCC may simplify clinical workflows and enhance patient safety.	B	7/9

Abbreviations: cSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mcSCC, metastatic cutaneous squamous cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

TABLE 3.

Efficacy Data (ORRs, CRs, and PRs) With Associated Median Duration of Follow-up From Pivotal and Long-term Trials for ICIs in the Treatment of laCSCC and mCSCC†

Agent	Study / Dataset	Cohort	N	ORR (%)	CR (%)	PR (%)	Median Duration of Follow up (Months)
Cosibelimab	Phase 1 pivotal trial	mcSCC	78	47.4	7.7	39.7	15.4
Cosibelimab	Phase 1 extended follow-up (≥2 yrs)	mcSCC	78	50	12.8	37.2	29.3
Cosibelimab	Phase 1 extended follow-up (≥2 yrs)	lacSCC	31	54.8	25.8	29	24.1
Cemiplimab	Phase 1 Expansion Cohorts (EMPOWER-cSCC)	mcSCC or lacSCC	26	50	0	50	11.6
Cemiplimab	Phase 2 Cohorts (EMPOWER-cSCC)	mcSCC	59	47.4	6.8	40.6	9.4
Cemiplimab	EMPOWER-cSCC-1 long-term analysis Groups 1 – 3	mcSCC or lacSCC	193	47.2	20.3	26.9	42.5
Pembrolizumab	KEYNOTE-629	lacSCC	54	50	16.7	33.3	14.9
Pembrolizumab	KEYNOTE-629	mcSCC	105	35.2	10.5	24.8	11.4
Pembrolizumab	KEYNOTE-629 extended follow-up	lacSCC	54	51.9	22.2	29.6	52.4
Pembrolizumab	KEYNOTE-629 extended follow-up	mcSCC	105	35.2	12.4	22.9	64.7

Abbreviations: CR, complete response; lacSCC, locally advanced cutaneous squamous cell carcinoma; ICIs, immune checkpoint inhibitors; mcSCC, metastatic cutaneous squamous cell carcinoma; N, number; ORR, overall response rate; PR, partial response
†Comparisons across therapies are descriptive only. No head-to-head studies are available, and differences in trial design, patient populations, endpoints, and follow-up duration should be considered when interpreting these data.

trial results to clinical practice. Current staging systems and guidelines, including those from the National Comprehensive Cancer Network (NCCN), American Joint Committee on Cancer (AJCC), and Brigham and Women's Hospital (BWH), employ divergent risk stratification approaches without consensus on what constitutes locally advanced disease.[26-28] This definitional ambiguity introduces heterogeneity in both clinical practice and research populations, complicating the interpretation and application of treatment efficacy data to individual patients. When considering cosibelimab therapy, alignment between individual patient disease characteristics and those of the laCSCC population enrolled in pivotal trials is an important consideration, as efficacy estimates may not uniformly generalize to all patients classified as having "locally advanced" disease in routine practice.

Statement 2: *The efficacy of the PD-L1 inhibitor, cosibelimab, in cSCC is comparable to that of PD-1 inhibitors in similar patient populations. (SORT Level A)*

Although head-to-head trials comparing ICIs in advanced cSCC are not available, evaluating cosibelimab efficacy relative to cemiplimab and pembrolizumab provides an important therapeutic context. Cemiplimab demonstrated ORRs of 50% in advanced cSCC (mCSCC and laCSCC combined) and 47% in mCSCC alone in its pivotal phase 1 expansion cohort and phase 2 study.[11] Long-term analysis after 42.5 months of follow-up showed an ORR of 47.2% across both disease stages.[29] Pembrolizumab in the KEYNOTE-629 trial demonstrated ORRs of 50.0% (laCSCC) and 35.2% (mCSCC), with an overall ORR of 40.3%.[12] Extended follow-up (52.4-64.7 months) showed ORRs of 51.9% and 35.2% in laCSCC and mCSCC cohorts, respectively (Table 3).[22]

Cosibelimab extended follow-up data (≥2 years) demonstrated ORRs of 50.0% in mCSCC and 54.8% in laCSCC, falling within a similar, and possibly higher, range compared to other ICIs. However, these comparisons require cautious interpretation given cosibelimab's limited long-term follow-up of approximately two years versus the nearly four to five years of mature data available for cemiplimab and pembrolizumab (Table 3).

Review of the pivotal trials confirms that all 3 agents were evaluated in clinically aligned patient populations: predominantly older adults with ECOG 0-1 performance status, strong male predominance, and advanced, unresectable cSCC stratified into locally advanced and metastatic cohorts (Table 4). This alignment supports meaningful contextual comparison and the conclusion that cosibelimab outcomes are comparable to those of PD-1 inhibitors in similar populations.

Although cosibelimab is the third ICI approved for cSCC, it is the only PD-L1 inhibitor. PD-1 inhibitors bind the PD-1 receptor on T cells, blocking interaction with both PD-L1 and PD-L2 ligands, while PD-L1 inhibitors bind the PD-L1 ligand, blocking interaction with PD-1 and B7.1, but preserving the PD-L2-PD-1

TABLE 4.

Comparison of Patient Populations Reported in Clinical Trials for Advanced cSCC Treated With Cosibelimab, Pembrolizumab, or Cemiplimab (Excluding Adjuvant Therapy Clinical Trial Data)†

Feature	Cosibelimab	Pembrolizumab (KEYNOTE-629)	Cemiplimab (EMPOWER-cSCC-1)
N	192	159	358
Cohorts	mcSCC / lacSCC	lacSCC / mcSCC	mcSCC / lacSCC
Age Range, years	71 – 77	72–75	71–76
Male, *n (%)*	19 – 59 (61.3% – 75.6%)	39 – 119 (72.2% – 76.2%)	48 – 130 (77.8% – 91.5%)
ECOG 0–1, *n (%)*	17 – 55 (54.8% - 70.5%)	32 – 101 (59.3% – 65.7%)	31 – 98 (51.3% - 61.0%)
PD-L1+ effect determined	Response not dependent on PD-L1+ status	Not specified	Response not dependent on PD-L1+ status
Prior systemic therapy, *n (%)*	1 – 7 (3.2% – 9.0%)	Not specified	5 – 33 (3.0% - 35.7%)
Follow-up duration, months	24–29 months	~52–64 months	~42.5 months

Abbreviations: cSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group Performance Status; lacSCC, locally advanced cutaneous squamous cell carcinoma; mcSCC, metastatic cutaneous squamous cell carcinoma; N or n, number of study subjects; PD-L1, programmed death-ligand 1
†Comparisons across therapies are descriptive only. No head-to-head studies are available, and differences in trial design, patient populations, endpoints, and follow-up duration should be considered when interpreting these data.

interaction.[18,19] In addition to PD-L1 pathway blockade, preclinical in vitro studies have demonstrated that cosibelimab may exhibit secondary mechanisms of action that distinguish it from PD-1 inhibitors. Cosibelimab is an unmodified immunoglobulin G1 (IgG1) antibody with a functional Fc domain, which in vitro has been shown to mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[18,19] Through ADCC, natural killer cells are activated to release cytotoxic molecules, resulting in direct lysis of tumor cells. Through CDC, engagement of the Fc region initiates the classical complement cascade, leading to membrane attack complex formation and lysis of target cells.[19] Pre-clinical studies indicate that these Fc-mediated effects, including natural killer cell activation and complement engagement, are not observed with PD-1 inhibitors such as cemiplimab and pembrolizumab, which are IgG4 isotype antibodies engineered to minimize Fc-mediated immune activation.[30,31]

These dual-secondary mechanisms of action may contribute to its efficacy, possible longevity against tumor resistance seen in PD-1 inhibitors, and safety profile. However, the potential contribution of ADCC and CDC likely varies across patients due to differences in Fc receptor expression, heterogeneous PD-L1 expression on tumor cells, and the immunosuppressive tumor microenvironment.[19] Whether the similar efficacy across agents represents a broader class effect of PD-L1 pathway blockade or is specific to cosibelimab remains unclear and warrants further investigation through direct comparative studies.

Statement 3: *Cosibelimab has a comparable safety profile and is characterized by a lower level of high-grade adverse events compared to PD-1 inhibitors based on available data. (SORT Level A)*

The safety profile of cosibelimab has been evaluated through up to 2 years of follow-up. In the pivotal phase 1 trial (78 patients with mCSCC), 52.6% experienced grade ≥3 treatment-emergent adverse events (TEAEs), with no grade 4 or 5 TEAEs reported. Immune-related adverse events (irAEs) occurred in 23.1% of patients; only 2.6% experienced grade 3 irAEs, and no grade 4 or 5 irAEs occurred. There were no treatment-related deaths.[15]

Extended follow-up (≥2 years; 192 patients with mCSCC and laCSCC) demonstrated that 32.8% experienced serious TEAEs and 45.3% experienced grade ≥3 TEAEs. irAEs occurred in 27.6% of patients, with grade 3 events in 3.6%. Permanent discontinuation due to TEAEs occurred in 6.3%. Notably, no grade ≥3 pneumonitis, colitis, hepatitis, nephritis, or endocrinopathies were observed, and no grade 4 or 5 irAEs occurred. Adverse events led to death in 3.1% of patients, though all were considered unrelated to treatment.[14]

By comparison, cemiplimab long-term data showed 38.9-43.6% serious TEAEs, 45.5-49.2% grade ≥3 TEAEs, and 10.4-13.9% permanent discontinuation rates. Grade ≥3 irAEs occurred in 10.7-19.2% of patients, most commonly pneumonitis, autoimmune hepatitis, colitis, and diarrhea. TEAEs led to death in 2.6–8.5% of patients.[29] Pembrolizumab data from KEYNOTE-629 showed 70.4% TEAE incidence, with grade ≥3 and serious TEAEs in 11.3% and 10.1%, respectively. Permanent discontinuation occurred in 8.8%, grade ≥3 irAEs in 8.8%, and TEAEs led to death in 1.3%.[29]

These data suggest cosibelimab may offer improved safety and tolerability while maintaining efficacy. This is supported by a systematic review and meta-analysis of 125 trials (20,128 patients) showing PD-1 inhibitors were associated with significantly higher grade ≥3 treatment-related adverse events than PD-L1 inhibitors (OR 1.58; 95% CI 1.00-2.54) and higher rates of pneumonitis and hypothyroidism.[25]

Critical interpretive considerations must be noted. The minimum incidence required for an AE to be listed in the package insert differs among ICIs for cSCC. Cosibelimab includes AEs occurring in ≥10% of patients, cemiplimab includes those in ≥15%, and pembrolizumab lists only AEs occurring in ≥20% of patients.[32-34] These differences in reporting thresholds mean the cosibelimab package insert captures a greater number of low-frequency events, potentially creating the appearance of a broader adverse event profile while underestimating the true breadth for the comparator agents. Direct comparison of adverse event frequencies based solely on package insert data may therefore be misleading.

Additionally, while studied in generally comparable populations, the depth of safety evidence differs. PD-1 inhibitors have more mature datasets enabling clearer identification of uncommon or delayed toxicities, whereas the cosibelimab evidence base is earlier in development. The absence of grade 4 and 5 irAEs in available data from cosibelimab trials should not be interpreted as confirmation that such events do not occur; rather, the data suggest they are uncommon within the current follow-up window of two years. Ongoing monitoring and future long-term data remain essential to fully characterize cosibelimab's safety profile.

Statement 4: *Given the current evidence, the absence of grade 4 and 5 immune-related adverse events with cosibelimab is clinically meaningful. (SORT Level A)*

irAEs represent a significant concern with checkpoint inhibitor therapy. ICIs enhance T-cell activity not only against tumors but also against normal tissues, causing effects ranging from dermatologic manifestations to colitis, hepatitis, thyroid dysfunction, pneumonitis, and neurological complications.[35] Grade 4 events are life-threatening and require urgent intervention; grade 5 events result in death.[36,37] NCCN and American Society of Clinical Oncology (ASCO) guidelines recommend permanent discontinuation of immunotherapy for grade 4 or higher irAEs or for toxicities that fail to resolve with immunosuppression.[37,38] Prevention of these severe toxicities therefore has meaningful implications for patient safety, treatment duration, and mortality.

Clinical trial data for cosibelimab spanning approximately two years have documented no grade 4 or 5 and only 2.6% grade 3 irAEs,[14,15] contrasting with PD-1 inhibitors where grade ≥3 irAEs occurred in 8.8–19.2% of patients.[22,29] This difference extends beyond statistical measures to tangible patient care impacts: reduced mortality risk, fewer hospitalizations, less treatment interruption and/or discontinuation, and avoidance of long-term sequelae.

In practice, there is a critical difference between avoiding versus managing severe toxicities. For advanced cSCC, where treatment options have historically been limited, early detection and aggressive management of treatment-related adverse events has been necessary to maintain patients on life-saving therapy.[38] Cosibelimab offers an alternative paradigm: selecting a treatment that is less likely to cause severe toxicities. This avoidance-oriented approach may be particularly valuable when intensive monitoring is challenging, specialist access for irAE management is limited, patient comorbidities increase vulnerability to severe toxicities, or quality of life and tolerability are high priorities.[38]

Statement 5: *Given its favorable adverse event profile, cosibelimab may provide a clinical advantage compared to other systemic therapies for mCSCC and laCSCC. (SORT Level A)*

The safety profile of cosibelimab, particularly the absence of grade 4 or 5 irAEs in available studies, may translate into meaningful real-world clinical advantages for any patient undergoing treatment for laCSCC or mCSCC. While pembrolizumab and cemiplimab demonstrate comparable efficacy with similar objective response rates, these PD-1 inhibitors are associated with higher rates of grade ≥3 irAEs.[11,12,14,15,22,29] This distinction becomes particularly relevant in settings where prevention, rather than management, of severe toxicities offers tangible benefits.

Community practices, rural healthcare settings, and facilities without immediate subspecialist access may find the lower irAE rate particularly advantageous. Registry data show longer time to irAE diagnosis in private practices versus university hospitals.[39] One community-based study found that only 65% of patients with ICI-related colitis received subspecialist evaluation.[40]

Cosibelimab's safety profile may also expand treatment eligibility to patients who might otherwise be marginal candidates for checkpoint inhibition: elderly patients, those with multiple comorbidities, and patients with limited ability to attend frequent monitoring visits.[38] Notably, median ages in cSCC ICI trials ranged from 71–76 years (Table 4).[11,12,14,15,22,29] When quality of life and tolerability are high priorities or specialist access for irAE management is limited, cosibelimab's safety advantages may represent a clinically meaningful difference in benefit-risk assessment.

Statement 6: *The reduced risk for grade 4 and 5 adverse events with cosibelimab for the management of mCSCC and laCSCC may simplify clinical workflows and enhance patient safety. (SORT Level B)*

The potential for reduced severe adverse events with cosibelimab may simplify clinical workflow management and patient safety monitoring protocols. This statement received supermajority approval (7/9), reflecting some panel variability

regarding the strength of supporting evidence. The workflow simplification recommendation is driven largely by expert consensus rather than direct clinical study evidence. However, available data showing a favorable adverse event profile with lower high-grade events and no grade 4 or 5 irAEs suggest patients may remain on cosibelimab longer due to improved safety and tolerability, resulting in fewer treatment interruptions and discontinuations.[38]

Extended follow-up data from cosibelimab clinical trials demonstrated increasing complete response (CR) rates over time in both mCSCC and laCSCC cohorts. In the mCSCC cohort, CR rates increased from 7.7% to 12.8%, accompanied by a decrease in partial responses (PRs) from 39.7% to 37.2%, suggesting conversion of partial to complete responses with continued therapy. Similarly, in the laCSCC cohort, CR rates increased substantially from 9.7% in the primary analysis to 25.8% with extended follow-up, alongside a reduction in PRs from 38.7% to 29.0%.[14,15] Collectively, these findings support the clinical benefit of maintaining patients on uninterrupted treatment to allow for deepening of responses over time.

CONCLUSION

A comprehensive expert panel literature review developed six consensus statements on cosibelimab's efficacy and safety in managing laCSCC and mCSCC. The panel concluded that cosibelimab demonstrates comparable efficacy to current PD-1 inhibitors, with ORRs of 50–54.8% across mCSCC and laCSCC cohorts. The absence of grade 4 and 5 irAEs in available studies was noted to be clinically meaningful and may confer advantages to any patient undergoing treatment for laCSCC or mSCC, and especially to those in settings with limited capacity for intensive adverse event monitoring.

While cosibelimab's total evidence base remains more limited than that of cemiplimab and pembrolizumab, and longer-term follow-up is needed, available data support cosibelimab as an effective and relatively well-tolerated option for patients with advanced cSCC who are neither surgical nor radiation candidates. These consensus recommendations can guide clinicians in treatment decision-making as they integrate this newest therapeutic option into practice for advanced cutaneous squamous cell carcinoma.

DISCLOSURES

Brooke Bartley MD, Angela Rosenberg DO, Daniel Groisser MD, and Lauren DeBusk MD have no conflicts of interest to disclose. Aaron S. Farberg MD is on advisory boards for Ortho Dermatologics, Regeneron Pharmaceuticals, Sun Pharma, and Castle Biosciences, Inc. Scott M. Dinehart MD serves as a speaker and consultant for Genentech, Regeneron Pharmaceuticals/Sanofi, Castle Biosciences, and Sun Pharma; and participates in clinical research with 3M Pharmaceuticals, Eli Lilly, Pfizer, Horizon Therapeutics, Leo Pharma, Galderma, Dermira, Amgen, Connetics, Novartis, Genentech, Sanofi, Genmab, Dow Pharma, Abbott Laboratories, Dermik, MedImmune, Rapt Therapeutics, Aclaris Therapeutics, AbbVie, Biocon, Incyte, Castle Biosciences, Bristol Myers Squibb, Xencor, Merck, Ventyx, Daiichi Sankyo, Brexogen, Apogee, Regeneron Pharmaceuticals, and Sun Pharma. Shannon C. Trotter DO has a professional relationship with Castle Biosciences, Inc. Lindsay Ackerman MD is a consultant/advisor, speaker, or investigator for AbbVie, Alumis, Amgen, Apogee, Apollo, ArGEN-X, Artacus, AstraZeneca, Biofrontera, Boehringer-Ingelheim, Bristol Myers Squibb, Castle Biosciences, ChemoCentryx, Corevitas (Corrona), DermTech, Eli Lilly, Exact Biosciences, GlaxoSmithKline, Helsinn, Incyte, Janssen, Kyowa Kirin, Leo, Merck, Mindera, Novartis, Pfizer, Regeneron, Sanofi, Soligenix, Sun Pharma, Takeda, Timber, Trevi, UCB, Veradermics, and ZuraBio. Todd Schlesinger MD FAAD FASMS is an investigator and/or consultant for AbbVie, Almirall, Apogee, Arcutis, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly, Flint Clinical, Genentech, Janssen, LEO Pharma, Oruka, Pfizer, Regeneron, Sun Pharma, Verrica, and UCB; served as an investigator for AbbVie, Allergan, Almirall, Arcutis, Aslan, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, Concert (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, Highlightll, Incyte, Janssen, Nimbus Therapeutics, Medicus, Novartis, Processa, Prolacta, Regeneron, Sanofi, SkinCure Oncology, Takeda, Trevi, and Verrica; is a shareholder in Bristol Myers Squibb, Chronicle Medical Software, Derma-Gene, Eli Lilly, Propedix and Remedly; has served as a consultant for Beiersdorf, Estee Lauder, Dermsquared, HTL Biotechnology, LaRoche Posay, L'Oreal, MJH Life Sciences, and RBC Consultants; and has received salary from Avant-Health. James Q. Del Rosso DO has received grants from JDR Dermatology Research and personal fees from James Q. Del Rosso DO, LLC during the conduct of the study. He has received personal fees from Galderma, Almirall, Sun Pharma, Vyne, Leo Pharma, Sente, Journey, Main Pharma, Cutera, Bausch (Ortho), Amgen, Arcutis, Biofrontera, Blue Medicines, Bluefin, Botanix, Cage Bio, Incyte, Organon, MoonLake, Pelthos, Regeneron, Sanofi, Takeda, and Verrica outside the submitted work. Mark Lebwohl MD has received grants and/or research funding from AbbVie, Arcutis, Avotres, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Clexio, Dermavant Sciences, Eli Lilly and Company, Incyte Corporation, Inozyme, Janssen Research and Development LLC/Johnson & Johnson, Oruka, Pfizer Inc., Sanofi-Regeneron, and UCB; serving as a consultant for AbbVie, Added Health, Aikium, Almirall, AltruBio Inc., Alumis, Amgen, Apogee, Arcutis Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Edessa, Eli Lilly and Company, Evommune Inc., Forte Biosciences, Galderma, Genentech, Janssen/Johnson & Johnson, Incyte Corporation, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, MoonLake, Oruka, Pfizer

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Longer Pembrolizumab Therapy Reduces Mortality in Stage III and IV Melanoma: A TriNetX Study

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ABSTRACT

Background: Melanoma is the leading cause of skin-cancer-related mortality worldwide. Anti-programmed cell death protein-1 therapies, including pembrolizumab, play a critical role in treating advanced melanoma. However, the optimal treatment duration remains undetermined.

Objective: To evaluate whether longer durations of pembrolizumab therapy improve overall mortality in stage III and stage IV melanoma.

Methods: We conducted a retrospective cohort study using the TriNetX platform, including 234 patients who received 24+ months of therapy (long-term) and 796 patients who received 12 to 24 months (intermediate-duration). A cohort of 746 patients who received pembrolizumab for 7 to 10 months (short-term) served as the comparison group. Mortality, hospitalizations, serum lactate dehydrogenase (LDH) levels, and adverse events were analyzed over 10 years using Cox proportional hazards regression with propensity score matching.

Results: Long-term therapy significantly reduced overall mortality (HR = 0.41, 95% CI: 0.27–0.62) compared with short-term therapy. Intermediate-duration therapy also reduced mortality (HR = 0.47, 95% CI: 0.37–0.60) and hospitalizations (HR = 0.74, 95% CI: 0.68–0.93). Differences in LDH levels and adverse events did not reach statistical significance.

Conclusions: Longer durations of pembrolizumab therapy reduces overall mortality in stage III and stage IV melanoma, reinforcing its safety and utility. Prospective studies are needed to confirm these findings.

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INTRODUCTION

Melanoma is the leading cause of skin cancer-related mortality worldwide.[1] Advances in anti-programmed cell death protein 1 (PD-1) therapies, such as pembrolizumab, have significantly improved survival outcomes in advanced melanoma.[2] However, the optimal duration of pembrolizumab treatment remains uncertain and real-world treatment durations vary.[3]

Pembrolizumab, administered via outpatient infusion every 3 or 6 weeks, has demonstrated significantly reduced mortality compared with standard chemotherapy in advanced melanoma.[2,3] The KEYNOTE trials, including KEYNOTE-001 and KEYNOTE-006, were designed to assess the safety and efficacy of pembrolizumab.[2,3] These trials relied on physician-determined clinical responses to guide treatment discontinuation rather than a predefined treatment duration.[4] Although the median treatment duration in the KEYNOTE-001 trial was approximately 5.6 months, a subset of patients continued pembrolizumab therapy safely beyond 12 months, with durable clinical responses.[2,3] Similarly, the KEYNOTE-006 trial allowed treatment for up to 24 months, and some patients who completed the full course achieved long-term disease control.[5] However, these trials did not directly compare different pembrolizumab treatment durations, leaving unanswered the question of whether prolonged therapy provides further survival advantages.[5]

To address this gap, we conducted a large, retrospective cohort study using the TriNetX research network to evaluate the impact of pembrolizumab duration on overall mortality in stage III and stage IV melanoma. Specifically, we aimed to

assess whether extended durations of pembrolizumab therapy, particularly those exceeding 12 or 24 months, further reduce overall mortality in advanced melanoma compared with shorter durations. Our study provides real-world evidence that may inform clinical decisions regarding pembrolizumab duration.

Study Sample

Our study used data from the TriNetX Research Network, which comprises de-identified electronic health records (EHRs) from over 97 participating healthcare organizations within the United States. The network includes more than 100 million patient charts from diverse healthcare regions across the US, spanning from 2004 to the present. Patients were identified using standardized coding systems, including ICD-10 (International Classification of Diseases, 10th Revision), CPT (Current Procedural Terminology), and RxNorm codes.

We established 2 exposed cohorts of patients with stage III or stage IV melanoma (ICD-10: C43): one group that received 24 months of pembrolizumab therapy (RxNorm: 1657751) (long-term therapy) and another that received 12 months of pembrolizumab infusions (intermediate-duration therapy). The control cohort consisted of patients who received 7 to 10 months of pembrolizumab therapy (short-term therapy). Pembrolizumab therapy duration was estimated by dividing the total number of prescriptions a patient received by the expected number of doses per month (1.45 doses/month, based on a 21-day schedule). To minimize bias from individuals with a better pretreatment prognosis, we excluded patients who initiated therapy with stage I or II melanoma from all cohorts.

FIGURE 1. Flowchart for population selection using the TriNetX network.

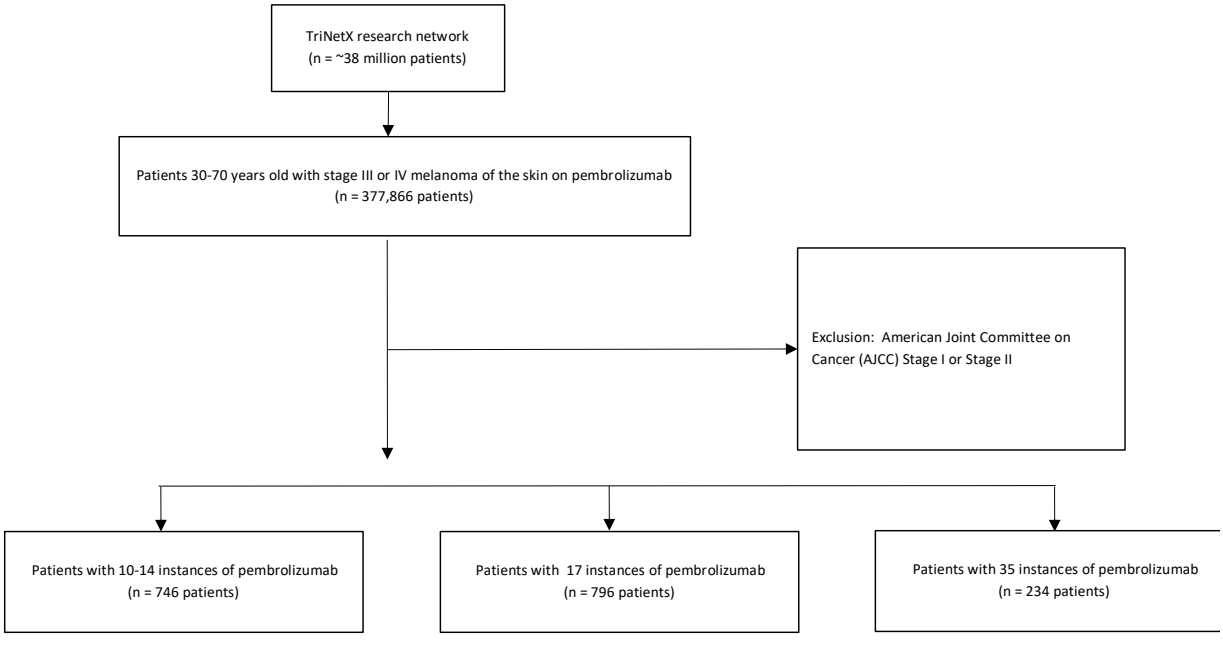
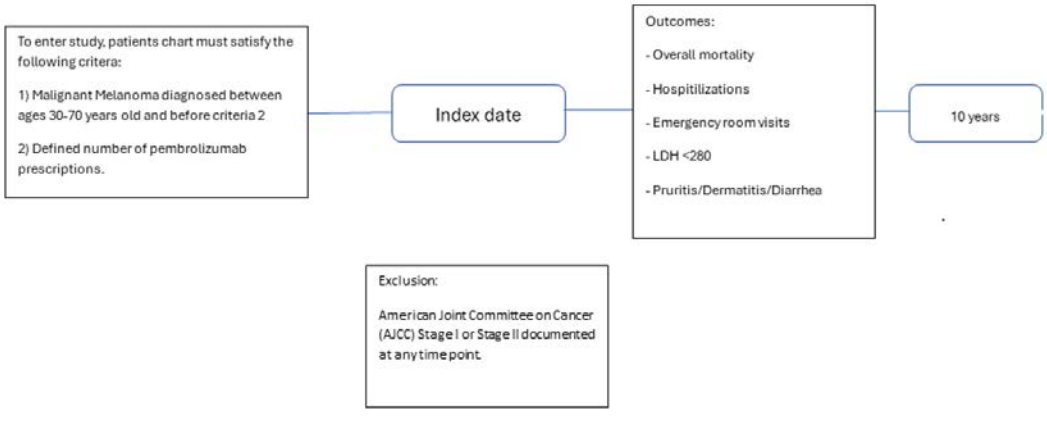


FIGURE 2. Timeline.



Measures

The medical records of patients in both the exposed and control cohorts were analyzed to compare differences in mortality, hospitalizations, emergency room visits, and serum lactate dehydrogenase (LDH) levels over a 10-year period. Additionally, differences in adverse events associated with pembrolizumab therapy, including pruritus, dermatitis, and diarrhea, were evaluated. A significant change in LDH levels was defined as achieving an LDH <280 U/L.

Hospitalizations were identified using CPT codes for inpatient consults (99221–99233) or critical care services (99291–99292). Emergency room visits were identified using CPT codes for emergency department services (99281–99285).

Statistical Analysis

To minimize confounding and ensure comparability between the exposed and control cohorts, propensity score matching (PSM) was performed using a 1:1 greedy nearest neighbor algorithm. The PSM model incorporated demographic, diagnostic, and prescription data, including age, gender, race, ethnicity, diabetes mellitus (ICD-10: E10–E11), tobacco use (ICD-10: Z72.0), and obesity (ICD-10: E66.9). Additionally, the presence of the BRAF mutation, a marker of poor prognosis in stage III or stage IV melanoma, was included in the PSM model. Cancer stage was also incorporated and balanced across cohorts.

The index date was defined as the date a patient completed a specified duration of pembrolizumab therapy. The analysis window began one day after the index date and extended for up to 10 years. Patients were censored if their last recorded clinical encounter occurred during the study period, indicating loss to follow-up.

To estimate risk, Cox proportional hazards models were applied, generating hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted using the TriNetX platform.

TABLE 1.

Baseline Characteristics After Propensity Score Matching and Before Index Date

	Intermediate-duration therapy[1]	Short-term therapy[2]	*P*-Value	Long-term therapy[3]	Short-term therapy[2]	*P*-Value	Long-term therapy[3]	Intermediate-duration therapy	*P*-Value
n=before PSM	796	746	--	234	746	--	234	796	--
n=after PSM	771	711	--	226	226	--	229	229	--
Demographics									
Age at index (year), mean	57.8+-10.80	57.5+-11.00	0.81	55 +-9.1	56 +-9.50	0.54	55.2 +- 9.20	53.9 +-11.80	0.54
Body mass index, mean	29.2+-6.70	29.4+-6.70	0.83	29.2+-6.10	29.7+-7.70	0.73	28.9+-6.50	29.8+-7.20	0.57
Male %	59.30	60.70	0.80	59.70	56.50	0.71	63.00	57.40	0.55
White %	87.90	89.30	0.70	88.70	93.50	0.34	88.90	92.60	0.50
Hispanic or Latino %*	0	0	--	16.10	16.10	1.00	0	0	--
African American %*	7.10	7.10	1.00	16.10	16.10	1.00	18.50	18.50	1.00
Diagnosis (ICD-10)									
Diabetes (E08-E13) %	8.60	8.60	1.00	16.10	16.10	1.00	18.50	18.50	1.00
Tobacco use disorder (Z72.0) %	7.10	7.10	1.00	16.10	16.10	1.00	18.50	18.50	1.00
Nicotine dependence (F17.200) %	7.10	7.10	1.00	16.10	16.10	1.00	18.50	18.50	1.00
Obesity (E66) %	14.30	12.90	0.72	16.10	16.10	1.00	18.50	18.50	1.00
Genetics									
BRAF %	16.10	16.10	1.00	18.50	0	0.001	18.50	0	0.001
Oncology (number of patients) Genetics									
Stage I	0	0	--	0	0	--	0	0	--
Stage II	0	0	--	0	0	--	0	0	--
Stage III	10	11	0.81	10	10	1.00	10	10	1.00
Stage IV	10	10	1.00	10	10	1.00	10	10	1.00

*Patients can identify as more than one race.
[1]12 months of pembrolizumab therapy.
[2]7–10 months of pembrolizumab therapy.
[3]24 months of pembrolizumab therapy.
PSM, propensity score matching.

TABLE 2.

Outcomes Over Ten Years									
	Intermediate-duration therapy[1]	Short-term therapy[2]	HR (95% CI)	Long-term therapy[3]	Short-term therapy[2]	HR (95% CI)	Long-term therapy[3]	Intermediate-duration therapy	HR (95% CI)
Overall mortality (n)	121	181	0.47 (0.37,0.60)	43	52	0.41 (0.27,0.62)	45	45	0.62 (0.41,0.94)
Hospitalizations[a] (n)	336	334	0.79 (0.68,0.93)	127	92	1.06 (0.81,1.40)	127	116	0.96 (0.75,1.24)
Emergency room visits[b]	235	235	0.79 (0.66,0.95)	104	68	1.15 (0.84,1.57)	104	88	1.03 (0.77,1.38)
LDH <280	128	114	0.96 (0.74,1.24)	41	31	1.00 (0.62,1.62)	42	46	0.81 (0.53,1.24)
Pruritus/Dermatitis/Diarrhea	104	99	0.91 (0.69,1.20)	50	32	1.19 (0.76,1.87)	52	37	1.25 (0.83,1.94)

[1]12 months of pembrolizumab therapy.
[2]7-10 months of pembrolizumab therapy.
[3]24 months of pembrolizumab therapy.
[a]CPT 99221–99233; 99291–99292
[b]CPT 99281–99285

RESULTS

Baseline Characteristics Before and After Propensity Score Matching

Among the 1,776 patients included in the study, 42.0% received short-term therapy, 44.8% received intermediate therapy, and 13.2% underwent long-term pembrolizumab therapy for stage III or stage IV melanoma. Each cohort was well matched, with comparable characteristics to the control cohort. The demographic distribution of patients receiving intermediate therapy was 89% from US regions (Northeast: 29%, Midwest: 15%, South: 21%, West: 24%), 7% from non-US regions, and 4% from unspecified regions. For long-term therapy, 93% were from US regions (Northeast: 34%, Midwest: 28%, South: 13%, West: 18%) and 7% from non-US regions. Among short-term therapy patients, 94% were from US regions (Northeast: 32%, Midwest: 21%, South: 20%, West: 21%), 5% from non-US regions, and 1% from unspecified regions.

In the analysis comparing intermediate therapy with short-term therapy, 771 patients were matched to an equal number of patients in the control group, with an average age of 53.9 years. Males comprised 57.4% of this cohort. Racially and ethnically, 92.6% identified as White, 18.5% as Black, and 0% as Hispanic or Latino. Comorbidities were also well matched, including diabetes mellitus (8.0%), tobacco use (7.1%), nicotine dependence (7.1%), and obesity (14.3% in the exposure group and 12% in the control group). Melanoma stages III and IV were equally represented at 10%. The BRAF mutation was present in 7.0% of the exposed group.

In the analysis comparing long-term therapy with short-term therapy, 226 individuals with a mean age of 55.0 years were matched to an equal number in the control group. Males comprised 59.7% of this cohort, while 88.7% identified as White and 16.1% as Black or Hispanic. Comorbidities, including diabetes mellitus, tobacco use, nicotine dependence, and obesity, were equally represented with 16% in each cohort. Melanoma stages III and IV were also equally distributed, with 10% in each group. The BRAF V600E mutation was identified in 16.1% of patients in both cohorts.

Lastly, a study comparing long-term therapy with intermediate therapy was performed, which included 229 patients. The average age was 55.2 years in the exposure group and 53.9 years in the control group. Males comprised 63% of the long-term group and 53% of the intermediate group. All medical diagnoses were equally represented, with 18.5% in both groups. The BRAF mutation was identified in 18.5% of the long-term cohort. Stage III and Stage IV melanoma were equally represented, with 10% in each cohort.

Outcomes

In the analysis comparing intermediate-duration therapy with short-term therapy, patients had a significantly reduced risk of overall mortality (HR=0.47 [95% CI 0.37–0.60]) and hospitalization (HR=0.79 [95% CI 0.68–0.93]). The proportion of patients successfully achieving a normal serum LDH level was not significantly different between the groups (HR=0.96 [95% CI 0.74–1.24]). There were no significant differences in pruritus, dermatitis, or diarrhea (HR=0.91 [95% CI 0.69–1.20]).

In the second analysis comparing long-term therapy with short-term therapy, patients experienced a statistically significant reduction in overall mortality with a HR=0.41 (95% CI 0.27–0.62). However, there were no significant differences in hospitalizations (HR=1.06 [95% CI 0.81–1.40]) or LDH levels (HR=1.00 [95% CI

0.62–1.62]). There were no significant differences in pruritus, dermatitis, or diarrhea (HR=1.19 [95% CI 0.76–1.87]) between the long-term and short-term cohorts.

In the third analysis comparing long-term therapy with intermediate therapy, patients experienced a significant reduction in overall mortality with an HR=0.62 (95% CI 0.41–0.94). There were no significant differences in hospitalizations (HR=0.96 [95% CI 0.75–1.24]) or LDH levels (HR=0.81 [95% CI 0.53–1.24]). There were no significant differences in pruritus, dermatitis, or diarrhea (HR=1.25 [95% CI 0.83–1.94]).

DISCUSSION

Our study demonstrates that extending pembrolizumab therapy beyond 12 months reduces overall mortality in stage III and stage IV melanoma. These findings contribute to the growing body of evidence supporting the safety and efficacy of extended PD-1 inhibition.[6] While pembrolizumab is often discontinued earlier in clinical practice, our results suggest that prolonged therapy may provide additional survival benefits.[2,3]

Beyond its impact on overall mortality, our study also evaluated common treatment-related adverse effects, including pruritus, dermatitis, and diarrhea.[6] Up to 80% of patients receiving pembrolizumab experience these adverse events; however, we found no significant differences in toxicity across treatment durations. These findings offer reassurance regarding the safety of prolonged therapy.[6]

Strengths and Limitations

A key strength of our study is its large sample size and the use of PSM, which ensured well-balanced cancer stages across treatment groups prior to analysis. This approach helped mitigate indication bias, where patients receiving longer treatment might have had more severe baseline disease. Despite this potential bias, our findings demonstrated significant reductions in overall mortality, reinforcing the benefits of prolonged therapy.

However, inherent limitations of database studies must be acknowledged. These studies establish correlation but not causation. One notable limitation is survival selection bias, which occurs when patients who lived long enough to receive extended pembrolizumab therapy are more likely to be included in the long-term treatment group. This bias may lead to an overestimation of the true survival benefit associated with prolonged therapy, as individuals who succumbed to disease earlier would not have had the opportunity to receive extended treatment. Additionally, immortal time bias may be present, as patients classified into the long-term therapy group had to survive at least 24 months to be included. This could lead to an overestimation of survival benefits, as patients who tolerated prolonged pembrolizumab therapy may have had less aggressive disease, while those who discontinued treatment earlier likely had a more unfavorable prognosis.

Another notable limitation is misclassification bias, which may arise from under-documentation or inconsistencies in disease staging. The method used to estimate pembrolizumab therapy duration could have also resulted in misclassification bias. Duration was approximated by dividing the total number of prescriptions recorded for each patient by the expected number of doses per month. While this approach provides a reasonable estimate, it assumes consistent adherence to the dosing schedule and does not account for potential dose delays, missed treatments, or alternate dosing schedules. Additionally, the concurrent use of undocumented treatments, including over-the-counter products, may introduce confounding factors.

Although we used serum LDH levels as a proxy for disease burden, an ideal assessment of real-world clinical response would incorporate a broader set of parameters. Nonetheless, LDH remains a reasonable prognostic marker in database studies, where access to detailed clinical data is often limited.

Another important consideration is the financial burden of prolonged pembrolizumab therapy, which was not addressed in our analysis. The cost, exceeding $11,000 per dose, along with insurer-imposed restrictions such as lengthy prior authorization and appeals processes, may limit access to extended treatment. These barriers could influence prescribing patterns and prevent some patients from receiving the duration of therapy most likely to maximize survival benefits.

Additionally, the prevalence of the BRAF mutation – a marker of poor prognosis –was higher in the long-term cohort compared with the short-term and intermediate cohorts. This imbalance may have biased comparisons toward worse outcomes in the long-term cohort, potentially underestimating the true survival benefit of extended pembrolizumab treatment. Lastly, mortality data from EHRs are inherently incomplete, as deaths occurring outside the hospital setting are often unrecorded, introducing variability into the dataset.

CONCLUSION

This study demonstrated that longer durations of pembrolizumab therapy reduces overall mortality in stage III and stage IV melanoma. These findings support a growing body of evidence highlighting the safety and efficacy of pembrolizumab therapy. Further prospective studies are needed to confirm these findings.

DISCLOSURES

The authors have no conflicts of interest to disclose. No funding has been received for the present study. 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.

Data Sharing Statement

TriNetX data and searches are all stored and performed on their proprietary platform and cannot be exported in a sharable format.

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Mackenzie Gipple formulated the hypothesis and performed the literature search. Neal Gupta performed the database search and conducted the statistical analysis using the TriNetX platform. Mackenzie Gipple and Neal Gupta wrote the main manuscript. Maile Ray, Ashley Shayya, and Sandra McGinnis helped interpret and formulate the data. Marc Cohen, Omobola Onikoyi, Jessica Feig, Jared Jagdeo, and Howard Maibach provided critical feedback and helped review the final manuscript. All authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

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Malassezia Folliculitis Presentation, Diagnosis, and Treatment: A Review of "Fungal Acne"

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ABSTRACT

Background: *Malassezia* folliculitis (MF), commonly referred to as "fungal acne" is a dermatological condition caused by colonization of the commensal fungus *Malassezia*, which turns pathogenic under certain conditions. MF presents as pruritic, erythematous papules and pustules and is often mistaken for other dermatological conditions, including acne vulgaris (AV). Interest in MF has intensified in recent years, likely due to social media trends, leading to concern regarding patients inappropriately applying antifungals without a confirmed diagnosis.

Methods: This narrative review summarizes the prevalence of MF, risk factors for the condition, MF pathogenesis, diagnosis, and treatment options.

Results: MF prevalence varies by geographic region and is higher in patients diagnosed with AV vs the general population. Risk factors include hot, humid weather, hair follicle occlusion, and immunocompromise. Increased sebum production, lipase activity, and inflammation contribute to the pathogenesis of both MF and AV. MF diagnosis includes clinical presentation and confirmatory tests such as direct microscopy and histopathology. The mainstay of treatment is antifungal medication, though given shared pathogenic mechanisms between AV and MF, acne topicals that target pathogenesis of both conditions, including benzoyl peroxide and retinoids, may be beneficial.

Conclusion: Clinical presentation of MF resembles that of AV and other skin conditions, leading to misdiagnosis, delays in treatment, and persistence of MF in patients for years. This underscores the need for appropriate diagnosis and timely treatment. Given shared pathogenic mechanisms between AV and MF, further investigation of acne topicals that target the pathogenesis of both conditions for the treatment of MF is warranted.

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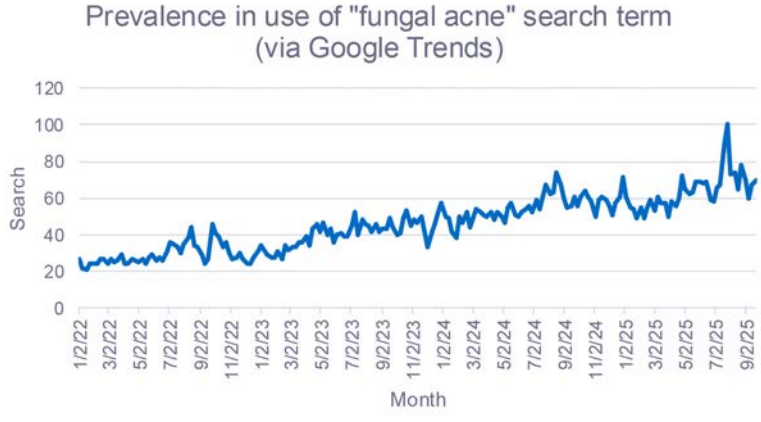
INTRODUCTION

Malassezia folliculitis (MF) is a lipid-dependent fungus that thrives on the lipid composition of sebum in the sebaceous glands of hair follicles and the stratum corneum.[1,2] *Malassezia* was previously referred to as *Pityrosporum* and was composed of only 3 species; however, at the end of the 1990s, the *Malassezia* genus was recognized, and the previous *Pityrosporum* fungi were incorporated into the genus.[3-5] To date, 18 species of *Malassezia* have been identified, with *M. restricta, globosa, furfur, sympodialis*, and *pachydermatis* frequently isolated from human skin.[6]

Although *Malassezia* is a commensal fungus and is the most prevalent fungal genus present on healthy skin,[2,3] it becomes pathogenic under certain conditions and is implicated in several skin disorders, including pityriasis versicolor, seborrheic

FIGURE 1. Frequency of "fungal acne" Google searches from January 2022 through September 2025.



Numbers represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of 0 means there were not enough data for this term.

dermatitis, atopic dermatitis, psoriasis, and folliculitis.[2,3,6] Often mistaken for other dermatological conditions, MF is a skin infection caused by the overgrowth of *Malassezia* in the pilosebaceous unit.[1,2] The clinical presentation of MF can be difficult to distinguish from acne vulgaris (AV), as patients with MF also present with papules and pustules, though there are unique features of the condition that can aid in diagnosis.[1,2,7]

In recent years, there has been an explosion of interest in *Malassezia* folliculitis (MF, commonly referred to as fungal acne), with a 119% rise in Google searches for "fungal acne" between 2022 (averaged over the year) and 2025 (averaged from January through September; Figure 1). This increased interest in MF may be attributable to social media beauty influencers amplifying discussions regarding the condition, as certain skincare trends, including the excess use of occlusive topical products ("slugging"),[8] can predispose skin to MF.[1] However, it is unlikely this increased interest reflects a sudden spike in prevalence of the condition, and although social media has increased awareness of MF, concern has been raised regarding the potential for patients to self-diagnose and inappropriately apply over-the-counter antifungals without a confirmed clinical diagnosis.

Here we review the prevalence, risk factors, pathophysiology, clinical presentation, diagnosis, and treatment of MF and discuss how the condition can be differentiated from AV.

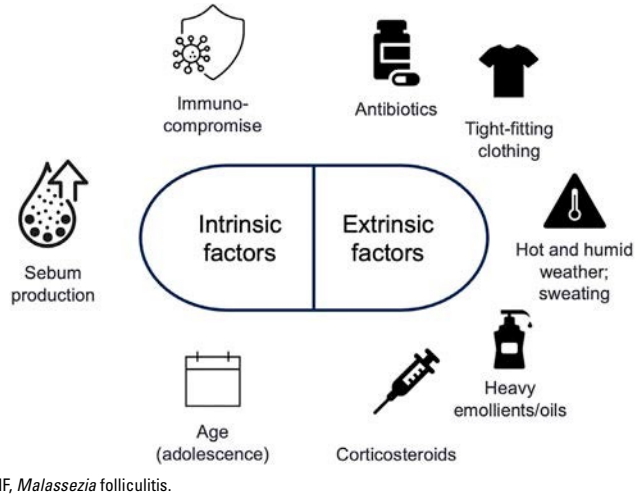
Prevalence

Comprehensive data regarding the prevalence of MF are lacking.[9] However, hospital studies report a range of rates, depending on the country, with a prevalence of 1% to 2% reported in China, 3% in Saudi Arabia, 4% in Turkey, and 16% in the Philippines.[6,9] MF occurs more frequently in hot, humid climates.[1,10] The condition is common in adolescents, presumably due to an increase in sebaceous gland activity during puberty,[1,3,11] and in middle-aged adults and males.[1,3,12,13] MF also frequently co-occurs with AV. A recent study conducted in Thailand found that in patients clinically diagnosed with AV, the prevalence of MF was 28.8%, significantly higher than the reported prevalence of MF in the general population.[7]

Risk Factors and Pathophysiology

While it is not completely understood how *Malassezia* transforms from a commensal organism to an opportunistic pathogen, both intrinsic and extrinsic risk factors may trigger MF development (Figure 2).[10] Intrinsic risk factors include age (young adult to middle age), increased sebum production as observed during adolescence, immunosuppression, and underlying conditions such as diabetes.[1,3,4,10] Exogenous risk factors include the use of antibiotic or corticosteroid medications, tight-fitting clothing, application of heavy emollients or oils, excessive sweating, and

FIGURE 2. Risk factors for the development of MF.



MF, *Malassezia* folliculitis.

hot or humid weather.[1,3,4,14] Genetic factors may also contribute to disease pathogenesis, such as predisposition to skin barrier dysfunction or inflammatory skin conditions such as atopic dermatitis.[3]

These risk factors may lead to disruption of the normal skin microbiome and/or contribute to hair follicle occlusion, leading to increased sebum production and an environment susceptible to an overgrowth of *Malassezia* (Figure 3).[3,5,10] This overgrowth eventually leads to infection of the hair follicle and subsequent inflammation.[10]

Malassezia is thought to contribute to inflammation via the organism's lipase and phospholipase enzyme activity.[7] Since *Malassezia* cannot synthesize long-chain fatty acids, it exploits its host's skin lipids as a source of energy and for use in its structural components.[10] The fungus integrates the fatty acids into its cell membrane to support growth and protect it from phagocytosis.[2] This use of the host's lipids may damage skin barrier function and induce irritation.[7] The lipase and phospholipase activity of *Malassezia*, which generates free fatty acid metabolites, may also cause keratinocytes to trigger the release of inflammatory cytokines via Toll-like receptor-2.[1,3,10] The fungus is also thought to interact with dendritic cells, macrophages, and myeloid cells, which are recruited to the skin via inflammatory signals, and is thought to activate complement cascades through both alternative and classical pathways.[10] These events result in the formation of clinical manifestations of the condition, follicular papules and pustules.[10]

Interestingly, *Malassezia* shares aspects of its pathogenesis with *Cutibacterium acnes* (*C. acnes*), the organism implicated in AV. *C. acnes* is also a common commensal skin organism that can turn pathogenic under particular conditions.[15] Increased levels of sebum and follicular occlusion are involved in the pathogenesis of both conditions.[3] As with *Malassezia*, *C. acnes* demonstrates lipase activity that can degrade sebum lipids and contribute to inflammation.[15] Both organisms can cause inflammation via interactions with keratinocytes.[2,7,10,16] Others have hypothesized that the ability of *C. acnes* to trigger epidermal lipid synthesis, resulting in increased lipid availability for *Malassezia* to thrive, may explain the coexistence of MF and AV.[6] Moreover, acne treatment with antibiotics can disrupt skin flora, further exacerbating MF.

As *Malassezia* is also implicated in seborrheic dermatitis and pityriasis versicolor, it is unsurprising that MF shares pathogenic mechanisms with these dermatological conditions as well.[17-19] Key

FIGURE 3. Pathogenic mechanisms of *Malassezia* in MF.

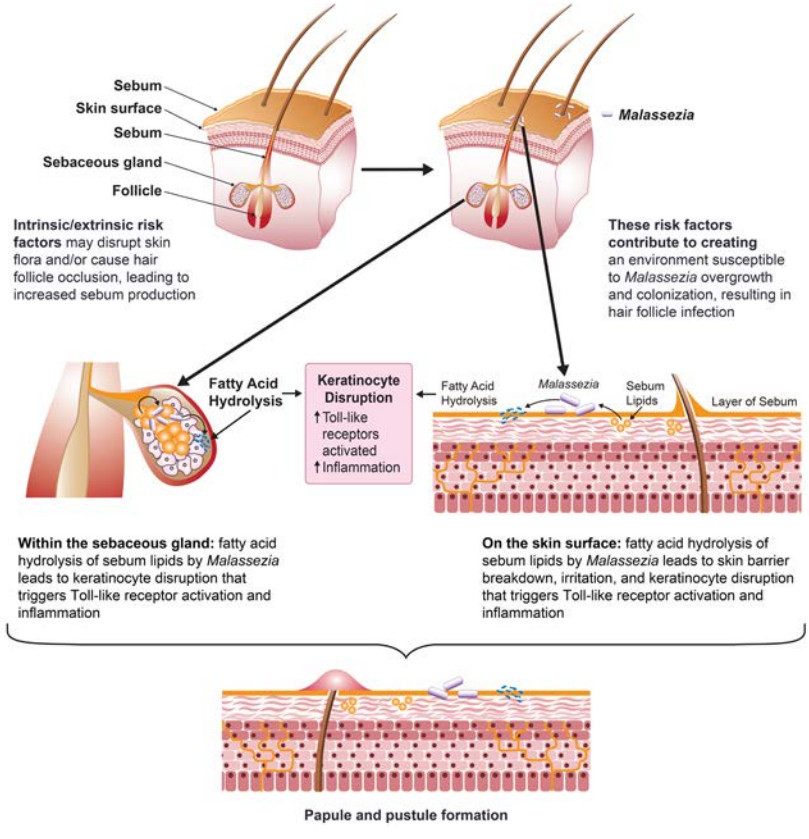


Figure adapted and modified from Jackson et al 2024.[17]
MF, *Malassezia* folliculitis.

aspects of pathophysiology that are shared across seborrheic dermatitis, pityriasis versicolor, and MF include increased lipid secretion through sebaceous glands, *Malassezia* colonization, and a subsequent inflammatory response.[17,20] The conditions also share similar risk factors, including immunocompromise and exposure to excessive heat.[17,19]

Clinical Presentation

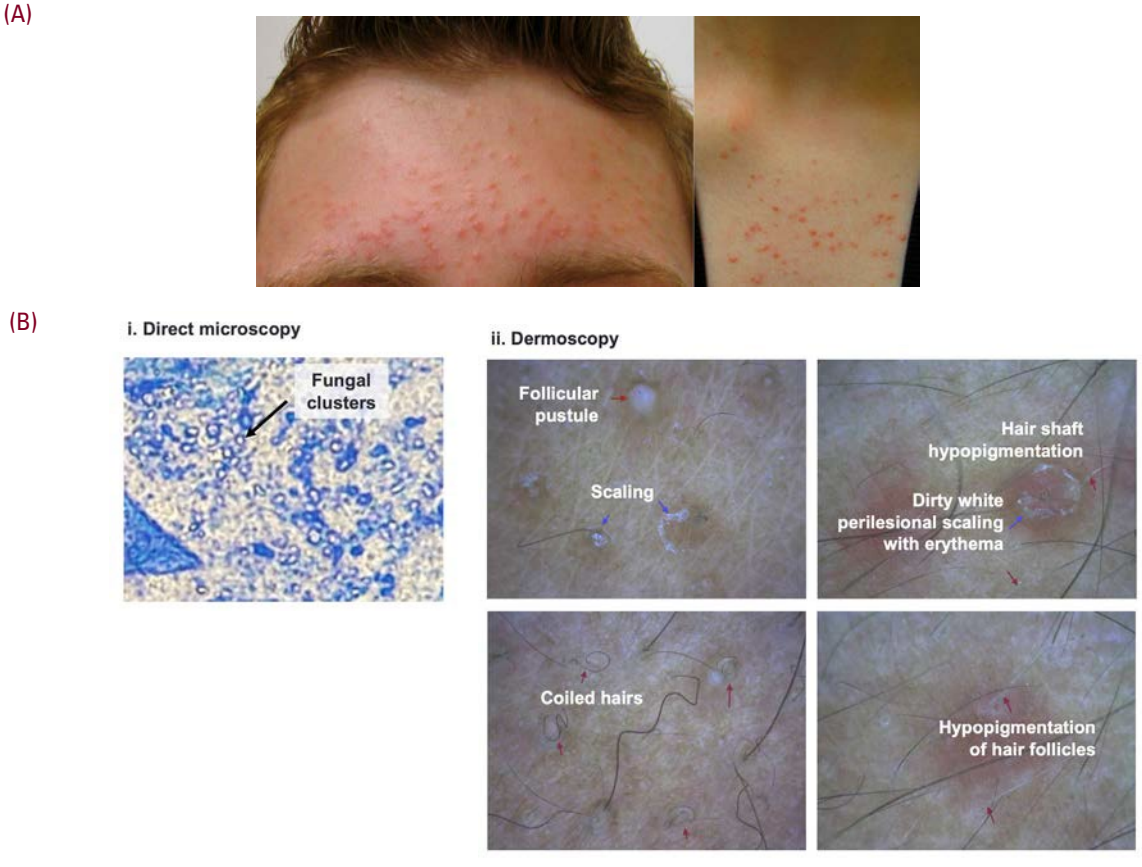
MF presents as numerous 1- to 4-mm monomorphic follicular papules intermixed with pustules on erythematous skin (Figure 4A).[1,3,9] The lesions are likely to be clustered and are commonly found in seborrheic regions of the skin, including the upper arms, chest, back, neck, and shoulders.[1,3,6,9,21] Facial and scalp distribution may be more common in children and adolescents compared with adults,[13,21] with facial lesions more commonly found on the chin and sides of the face rather than central areas.[1] Lesion eruption is rather sudden,[3] and pruritus is a key feature of the condition in most patients.[1,3,21] Excoriations, hyperpigmentation, and cysts may also be observed with MF.[1,9] Comedones and abscesses are not considered typical signs of the condition.[9]

Diagnosis

MF may persist for years if mismanaged,[1,6] underscoring the need for correct diagnosis. However, the condition is often misdiagnosed as AV or bacterial folliculitis because of its similar clinical characteristics. Recommendations for diagnosing MF developed by the European Academy of Dermatology and Venereology (EADV) Mycology Task Force MF working group include clinical assessment and direct microscopy to confirm clinical suspicion of the condition. It should be noted that these guidelines do not include direct microscopy as a diagnostic tool before beginning treatment with topical antifungals, which should be started solely based on clinical presentation of MF.[9]

With direct microscopy (Figure 4B),[6] pustule content is transferred onto a slide and dissolved in 10% to 20% potassium hydroxide (KOH).[9] Signs of MF with microscopy include unipolar budding yeasts and conidia.[9] Other staining techniques used to diagnose MF with microscopy include Gram staining, Methylene blue, May–Grünwald–Giemsa (MGG), Calcofluor white/Blancophor, and Chlorazol black E.[9,22] KOH staining is typically widely available, though differentiating fungus from bacteria may be

FIGURE 4. MF clinical presentation and diagnostic techniques.



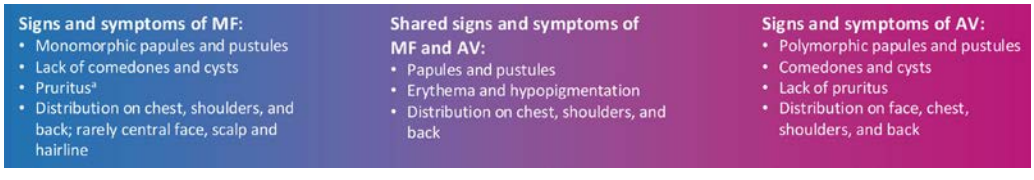
(A) Clinical presentation of MF (figure from Chalupczak and Lipner 2025).[26] MF presenting as numerous papules and pustules (forehead and upper chest in this case).
(B) MF presentation with various diagnostic techniques.
i. Direct microscopy of MF pustule fluid stained with methylene blue (40x) reveals fungal clusters (figure adapted from Martinez-Ortega et al 2024).[6]
ii. MF lesions viewed via dermoscopy (reprinted with permission from Jakhar et al 2019).[25]
MF, *Malassezia* folliculitis.

challenging with this technique.[6] Gram staining demonstrates high sensitivity and specificity, and though it is not as readily available as KOH, it is effective in differentiating between fungus and bacteria.[6] Methylene blue staining can enhance visibility of fungi if needed, while MGG staining can show cytological details and inflammation and is highly sensitive.[6] It is not, however, widely available, and would be best used in complex cases where both inflammation and fungi need to be visualized.[6] Calcofluor white demonstrates good visualization of fungi, though it requires fluorescence microscopy, which is not routinely available in all clinical settings.[6] Chlorazol black E is another simple fungal stain that can be used to identify budding yeasts observed with MF.

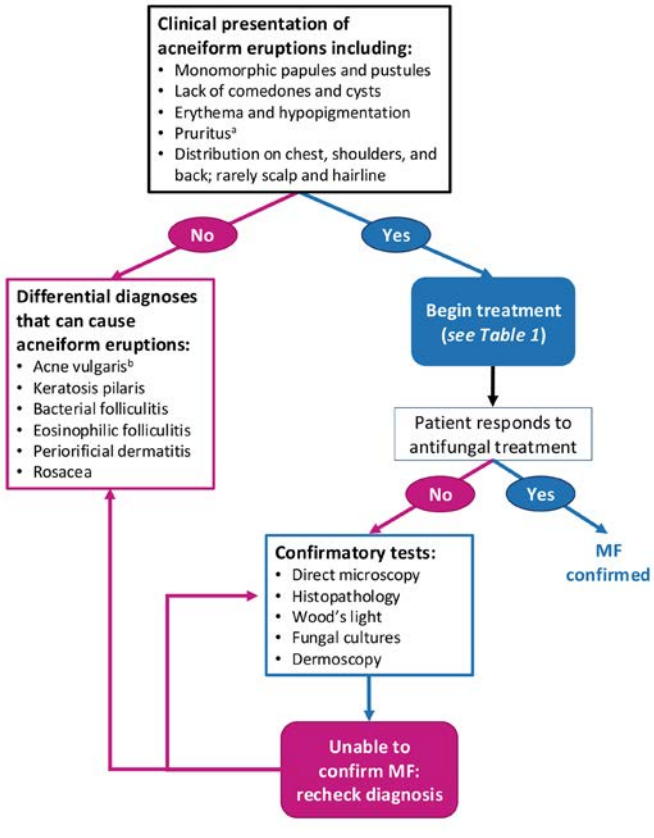
Other confirmatory diagnostic methods include histopathological analyses where a punch biopsy of the hair follicle is stained and examined for plugged follicles and inflammation; this is an invasive technique and may be best suited for confirming a diagnosis in patients where treatment has failed.[6]Though it is not considered a direct diagnostic tool for MF, Wood's light (also called Wood's lamp) is a cost-effective and quick option to distinguish MF from other conditions.[6] With this technique, upon exposure to UV light at 320- to 400-nm wavelength, MF lesions emit a green-yellow fluorescent light.[9,23,24] While fungal cultures can be conducted, they are not typically performed because of specific media requirements and the risk of false positives due to possible contamination of nonpathogenic *Malassezia* that may be collected from adjacent skin areas.[3,6,9] Dermoscopy can also be used as a noninvasive adjunctive method in the clinical assessment of lesions, but it is not considered a conclusive diagnostic method and requires laboratory confirmation.[6] With dermoscopy, MF appears as folliculocentric papules and pustules with surrounding erythema and perilesional, dirty white scaling in most cases (Figure 4B).[25] Coiled hair follicles with surrounding erythema and hypopigmentation of hair shafts may also be observed.[25] Finally, MF diagnosis can also be confirmed if rapid efficacy is observed with antifungal treatments.[1]

FIGURE 5. Differential diagnosis.

(A)



(B)



(A) Distinguishing signs and symptoms of MF and AV. (B) Differential diagnosis decision tree.
[a]MF in immunocompromised people may not be accompanied by pruritus. [b]MF can co-exist with acne vulgaris.
AV, acne vulgaris; MF, *Malassezia* folliculitis.

Distinguishing *Malassezia* Folliculitis From Acne Vulgaris

Differentiating MF from AV, though challenging, is key for the correct initiation of therapy, as use of antibiotics can disrupt skin flora, allowing for additional fungal overgrowth and exacerbation of MF.[1,6] Further complicating diagnosis is the potential for coexistence of AV and MF.[1,3,7] Key distinguishing features of MF from AV are the monomorphic nature of the eruptions, presence of pruritus, presence of frontal hairline and scalp involvement without central face involvement, and absence of comedones and cysts (Figure 5A).[1,3,9] Notably, under Wood's light (see "Diagnosis" section above), acne lesions fluoresce an orange-red color in contrast with the green-yellow fluorescence of MF lesions.[9,23,24]

Some cases of MF do not demonstrate a typical presentation and can appear like other conditions, including keratosis pilaris, bacterial folliculitis, eosinophilic folliculitis, and rosacea.[3,6,9,10] Bacterial folliculitis may cause fever or purulent discharge,[6] and patients with eosinophilic folliculitis may have high eosinophil blood counts.[9] Periorificial dermatitis lesions are more commonly distributed around the mouth and nose,[27] while rosacea typically presents on the cheeks, nose, chin, and central forehead.[28] Diagnostic tools mentioned above, including direct microscopy, dermoscopy, and histopathology, can be used as confirmatory tests to distinguish MF from other conditions (Figure 5B).

Treatment and Management

Table 1 summarizes EADV Mycology task force treatment recommendations in immunocompetent and immunocompromised patients with MF, with one of the following topical therapies recommended: azole antifungals; selenium sulfide; ciclopirox gel 0.77%, cream 1.5%, or shampoo 1.5%; propylene glycol 50% in water; or zinc pyrithione 1%.[3,9,14,29,30] Topical azoles include ketoconazole, econazole, clotrimazole, miconazole, and sertaconazole.[9] These topical medications may be recommended as first-line therapy in immunocompetent patients given their efficacy.[9,10,21,31] Although these agents typically have a favorable safety profile, patients should be advised to not initiate treatment without a confirmed clinical diagnosis of MF, as irritation and allergic reactions can occur.

In patients with MF refractory to topical treatments and in certain patients with immunosuppression, oral antifungals are recommended by the EADV working group, including fluconazole and itraconazole (Table 1).[3,6,9,10,14,29,30] These systemic therapies may also be considered to treat cases of widespread eruptions.[3] It should be noted that long-term use of oral antifungals carries the risk of adverse effects, such as hepatotoxicity, drug interactions, and adrenal hormone imbalances.[3] Fluconazole is generally preferred over itraconazole, as the latter has a risk of cardiac toxicity.[3] Combination of topical and oral antifungals may also be considered for patients with recalcitrant MF.

As MF tends to recur, a continued topical treatment regimen may be helpful in preventing relapses;[6,9,10] prophylaxis recommendations are included in Table 1. Lifestyle choices that can help in the prevention of relapses include avoiding heat, activities that predispose patients to sweating, tight-fitting clothing, or use of heavy emollients or oils that may cause hair follicle occlusion.[1,14] Prophylaxis may be more necessary during hotter summer months, as excessive sweating is a risk factor for MF.

TABLE 1.

MF Treatment Options Recommended by EADV Mycology Task Force

Therapy	Recommended Treatment Regimen	Recommended Prophylaxis Regimen
Topical therapies[a]		
Topical azole antifungals	Immunocompetent: QD or BID for 2-4 weeks	QW, BIW, or TIW
Selenium sulfide	Immunocompetent: QD for 3 days, then QW intermittently Immunocompromised: QD for 3 days, then QW intermittently	3 days, then QW
Ciclopirox gel 0.77%, cream 1.5%, or shampoo 1.5%	Immunocompetent: BID for 2–4 weeks Immunocompromised: BID for 2–4 weeks	QD for 4 weeks
Propylene glycol 50% in water	Immunocompetent: BID for 3 weeks Immunocompromised: BID for 3 weeks	BID for 3 weeks
Zinc pyrithione 1%	Immunocompetent: 1–2 daily for 2–4 weeks Immunocompromised: QD or BID for 2–4 weeks	QW, BIW, or TIW
Oral therapies[a]		
Fluconazole	Immunocompetent: 200 mg QD for 1–2 weeks or 200–300 mg weekly for 3 weeks Immunocompromised: 100–200 mg QD for 2–3 weeks or 300 mg weekly for 3 weeks	400 mg monthly
Itraconazole	Immunocompetent: 200 mg QD for 1–2 weeks Immunocompromised: 100–200 mg QD for 1–4 weeks	400 mg monthly

[a]In immunocompromised patients, the EADV Mycology Task Force working group on MF strongly supports a recommendation for oral therapies and moderately supports a recommendation for topical therapies.
BID, twice daily; BIW, twice per week; EADV, European Academy of Dermatology and Venereology; MF, *Malassezia* folliculitis; QD, once daily; QW, once per week.

Other Treatment Options for MF

In addition to antifungals, topical treatments for acne and seborrheic dermatitis may be well suited to the treatment of MF as pathogenic mechanisms of these diseases overlap.[1,9,30] A preclinical study by Ghannoum et al is currently underway investigating the efficacy of the fixed-dose, triple-combination acne topical clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel (CAB) and its 3 individual components against *Malassezia* species.[32] Benzoyl peroxide and adapalene, the constituents of CAB and well-established treatments for acne, have previously been used to treat *Malassezia*-induced infections. In a case study of a 25-year-old male patient with MF, treatment with intravenous itraconazole for 7 days and topical benzoyl peroxide 5% gel, with ketoconazole 2% cream for maintenance, was shown to be effective.[33] While IV treatment is rarely used for MF treatment, topical benzoyl peroxide may be beneficial due to its keratolytic and anti-inflammatory effects.[34,35] Topical retinoids, a mainstay of AV treatment, may treat MF due to their keratolytic and anti-inflammatory effects.[1] Studies have demonstrated the efficacy of adapalene 0.1% gel in the clinical resolution of pityriasis versicolor, a dermatological condition also caused by *Malassezia*.[36,37] While these studies were not conducted in patients with MF, the results suggest that adapalene may counteract the growth of *Malassezia* by targeting specific pathological mechanisms, including reducing the secretion of sebum through the sebaceous gland.[18] Hormonal therapies such as combined oral contraceptives, spironolactone, and clascoterone may also be considered because of their ability to reduce sebum production.[38,39] The acne topical dapsone 7.5% gel may also be beneficial against MF due to its anti-inflammatory effects and the inclusion of diethylene glycol monoethyl ether in its formulation,[40,41] which can disturb lipid packing in the skin,[42] thereby depriving *Malassezia* of its lipid energy source. Finally, roflumilast 0.3% foam for seborrheic dermatitis may be effective against MF due to its ability to reduce production of pro-inflammatory mediators.[43,44]

CONCLUSION

MF is commonly mistaken for other skin conditions such as AV, which could lead to a delay in treatment and persistence of symptoms. However, the recent increased awareness of MF among the public has raised concern about self-diagnosis and inappropriate use of antifungals. Further complicating diagnosis is the potential co-occurrence of MF with AV. Correct diagnosis of MF with clinical evaluations and laboratory confirmation is crucial for appropriate treatment and management with antifungals to alleviate symptoms and prevent recurrence. As MF and AV share aspects of pathogenesis, acne topicals that target the mechanisms of action of both conditions—including retinoids—may be beneficial, particularly in patients presenting with both diseases.

DISCLOSURES

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ORIGINAL ARTICLE

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Efficacy and Safety of Topical Metformin vs Kligman Formula in the Treatment of Melasma: A Split-Face Study

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ABSTRACT

Background: Melasma is an acquired pigmentary disorder characterized by symmetrical hyperpigmented macules and patches on sun-exposed areas, primarily the face. Kligman's formula, or "triple combination cream," is widely used but has potential side effects. Metformin, an oral anti-diabetic agent, possesses anti-inflammatory and anti-oxidative properties, suggesting its possible role in melasma treatment. This study aims to compare the efficacy and safety of topical Metformin with Kligman's formula in melasma treatment through a split-face design study.

Methods: This non-randomized, double-blind, split-face, comparative study included 57 patients with melasma over 12 weeks. Participants applied Kligman's formula to the right side of the face and topical metformin on the left side of the face at bedtime. Efficacy was assessed using melanin index measurements, physician global assessment, and patient satisfaction rates. Safety was evaluated by monitoring erythema, burning, and itching on both sides of the face.

Results: Of the 57 participants, 49 (86%) were female, and 8 (14%) were male. At baseline, the mean Hemi-MASI scores were 7.60 ± 3.44 (right) and 7.72 ± 3.45 (left). At month 3, scores significantly decreased to 3.30 ± 2.30 (right) and 3.81 ± 2.38 (left) (P<.001). The percentage reduction was significant on both sides, with 60.53 ± 15.65% (right) and 53.33 ± 14.88% (left).

Conclusions: While Kligman's formula demonstrated slightly better efficacy, both treatments reduced hyperpigmentation. Topical metformin could be an alternative for melasma patients with a lower risk of side effects.

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INTRODUCTION

Melasma is a frequent chronic pigmentary condition that is resistant to treatment, most commonly affecting Fitzpatrick skin types III to V.[1] Worldwide, melasma is one of the most prevalent dermatoses, varying from 9% to 50%.[2] The pathogenesis is due to increased melanocyte activity and melanin production, influenced by genetics, ultraviolet (UV) light, hormonal changes, and certain medications.[3] The disease appears as symmetrically arranged hyperpigmented patches and macules mainly on the face.[4] Clinically, melasma manifests as 3 facial patterns: centrofacial, malar, and mandibular. It can also be classified by Wood's lamp examination into epidermal, dermal, or mixed types based on the depth of melanin pigment.[1]

The gold standard in treating melasma is Kligman's formula, containing hydroquinone (HQ), but it may cause side effects like contact dermatitis, redness, post-inflammatory hyperpigmentation, permanent depigmentation, and ochronosis.[5] Metformin, primarily an anti-diabetic drug, has emerged as a potential treatment for melasma. It has been studied in various clinical trials for inflammatory skin conditions like hidradenitis suppurativa, acanthosis nigricans, psoriasis, acne, and allergic contact dermatitis, showing promising outcomes. In melasma, metformin reduces cyclic adenosine monophosphate (cAMP) levels, which helps lower melanin production in melanocytes by inhibiting key pathways.[6]

The first clinical trial by Banavase et al showed improvement of melasma using topical metformin in 13 out of 20 patients.[4] And metformin was found safer and equally effective when compared with the traditional triple combination creams. The study by Shokier DA showed statistically significant results after 3 months of treatment with the use of topical metformin.[3] AboAlsoud et al compared the efficacy of topical metformin 30% cream with triple combination cream.[7] However, no significant difference was seen in the 2 treatment options regarding the treatment of melasma.

The rationale for our study was to assess the efficacy of metformin in comparison to Kligman's formula using a split-face design, thus minimizing the inter-individual variations that could act as confounding factors.

MATERIALS AND METHODS

The study was conducted over a period of one year at the Dermatology Outpatient Department of Ghurki Trust Teaching Hospital, Lahore. Both male and female patients aged 16 to 60 years, having mild to moderate melasma and having not undertaken any treatment for melasma in the previous 14 days, were included in the study. Pregnant or lactating women, those taking oral contraceptive pills or phenytoin, and individuals with any other inflammatory skin conditions were excluded from the study. A sample size of 66 patients was determined (95% confidence interval, 80% test power, level of significance of 0.05, based on an average MASI score of 7.81 ± 5.32). Participants were selected through non-probability convenience sampling.

Initially, 66 patients were enrolled in the study. However, 9 patients were lost to follow-up during the first month, leaving a final cohort of 57 participants. Efficacy was defined as greater than 50% mean reduction of the hemi-facial MASI after the treatment. Safety was assessed by the absence of side effects such as erythema, burning, itching, hyperpigmentation, permanent depigmentation, ochronosis, and systemic side effects.

Procedure of Data Collection

The study was started after taking permission from the institutional ethical committee. At the baseline visit, informed consent was obtained from each patient, a consent form was signed, and a written, detailed Proforma was completed. Patients were examined, and photographs were taken at baseline prior to treatment and monthly throughout the 3-month treatment period. Physician global assessment was done, and their satisfaction levels were evaluated during each visit. Melasma severity was measured using the Melasma Area and Severity Index (MASI) and calculating the Hemi-facial MASI scores on both sides of the face. Additionally, the Dermatological Life Quality Index (DLQI) was assessed at baseline and 3 months post-treatment. Adverse effects of the 2 drugs were assessed with each follow-up and were efficiently managed.

Data Analysis

All the data were entered and analyzed using SPSS version 27. For quantitative variables, mean and standard deviation were calculated, while for qualitative variables, frequency and percentages were computed. The Kolmogorov test was applied to test the normality of the data. The Wilcoxon sign test was applied to measure the significant difference in MASI and hemi MASI score from baseline to month 3, while the chi-square test of independence was applied to test the association between patient satisfaction and global assessment scale at different intervals. Spearsman Correlation was applied to test the correlation between the percent reduction in h-MASI score on the left and right sides and patient satisfaction at month 3.

RESULTS

The current study included a total of 57 patients, out of whom the majority (86%) of the participants were females, and the mean age was 32.63 years, ranging from 20 to 46 years. Most of the participants (61.4%) were married, and the duration of disease varied, with 68.4% of participants experiencing melasma for 1 to 5 years. Prior treatment for melasma was reported by 86% of the participants, while 31.6% had a family history of the condition. The majority of participants (86%) had no history of painkiller use. None of these demographic variables was found to be statistically significant in relation to the reduction in hemi-MASI scores. Table 1 shows the demographic characteristics and clinical data of all patients.

TABLE 1.

Demographic and Clinical Parameters		
Variables	**N (%)**	**M (SD) Range**
Gender		
Male	8 (14.0)	--
Female	49 (86.0)	--
Age (years)	--	32.63 (6.64) 20-46
Marital Status		
Married	35 (61.4)	
Unmarried	22 (38.6)	
Duration of Disease		
<1 year	6 (10.5)	--
1-5 years	39 (68.4)	--
5-10 years	12 (21.1)	--
Prior Treatment		
Yes	49 (86.0)	--
No	8 (14.0)	--
Family History		
Yes	18 (31.6)	--
No	39 (48.6)	--
Pain Killer History		
Yes	8 (14.0)	--
No	49 (86.0)	--

TABLE 2.

Hemi-Melasma Area and Severity Index at Baseline and Month 3			
Clinical Parameter	Month 1	Month 3	*P*-Value
Hemi-MASI Score (Rt)	7.60 ±3.44	3.30 ±2.30	<.001
Hemi-MASI Score (Lt)	7.72 ±3.45	3.81 ±2.38	<.001

A comparative evaluation of various clinical parameters was conducted over 3 months. The Hemi-Melasma Area and Severity Index (h-MASI) scores showed significant improvement on both the right and left sides of the face. Table 2 shows that the right side observed a reduction in the mean score from 7.60 ± 3.44 at baseline to 3.30 ± 2.30 at 3 months (*P*<.001), and the left side showed a similar improvement from 7.75 ± 3.45 to 3.81 ± 2.38 (*P*<.001). Clinical improvements were observed as illustrated in Figures 1 to 4, comparing melasma severity at baseline and after 3 months of treatment with both therapies.

FIGURE 1. Right side (Kligman's formula) at Baseline and month 3.

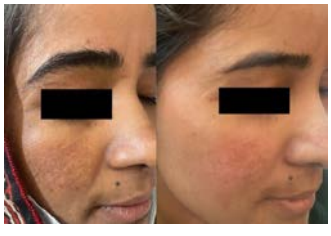


FIGURE 2. Left side (topical Metformin) at baseline and month 3.

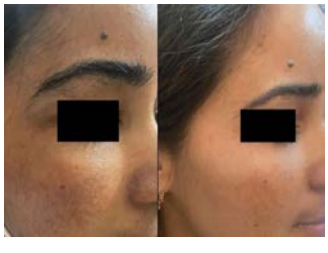
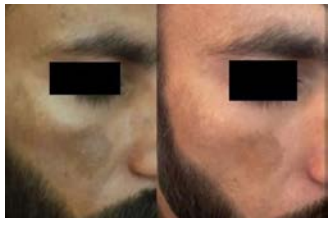


FIGURE 3. Right side (Kligman's formula) at baseline and month 3.

FIGURE 4. Left side (topical Metformin) at baseline and month 3.



While assessing the **Physician Global Assessment (PGA)** scale, there was a significant change in the outcomes over the 3-month period. The number of patients rated as "Good" and "Excellent" increased significantly on both sides, with the right side showing a more dramatic improvement. On the left side, the number of patients rated as "Poor" dropped substantially by the third month (Table 3).

Patient satisfaction rate improved over time on both sides. The right side showed an increase in satisfied patients from 12.3% at the 1st month to 68.4% by the 3rd month. On the left side, satisfaction increased from 12.3% to 47.4%. The number of dissatisfied patients dropped significantly, particularly on the left side (Table 4).

TABLE 3.

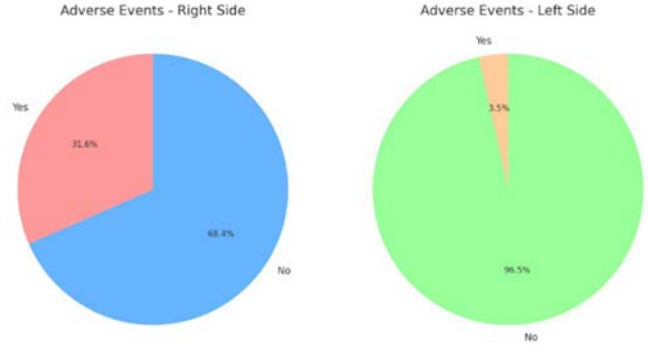
Physician Global Assessment Scale				
Physician Global Assessment	Right Side		Left Side	
	Month 1	Month 3	Month 1	Month 3
Excellent (76%-100%)	5 (8.8%)	9 (15.8%)	1 (1.8%)	3 (5.3%)
Good (51%-75%)	8 (14.0%)	35 (61.4%)	9 (15.8%)	28 (49.1%)
Fair (26%-50%)	38 (66.7%)	11 (19.3%)	21 (36.8%)	21 (36.8%)
Poor (0%-25%)	6 (10.5%)	2 (3.5%)	26 (45.6%)	5 (8.8%)

TABLE 4.

Patient Satisfaction Rate						
Patient Satisfaction	Right Side			Left Side		
	Month 1	Month 3	*P*-Value	Month 1	Month 3	*P*-Value
Very satisfied	1 (1.8%)	1 (1.8%)	--	0 (0%)	0 (0%)	--
Satisfied	7 (12.3%)	39 (68.4%)	--	7	28 (49.1%)	--
Neutral	(12.3%)	27 (47.4%)	--	21 (36.8%)	21 (36.8%)	--
Dissatisfied	34 (59.6%)	12 (21.1%)	0.071	28 (49.1%)	22 (38.6%)	0.003
	14 (24.6%)	5 (8.8%)	--	22 (38.6%)	6 (10.5%)	--

FIGURE 5. Dermatology Life Quality Index (DLQI) scores at months 1 and 3 of treatment.

FIGURE 6. Comparison of adverse events on the right (Kligman's formula) and left (topical Metformin) sides of the face.



The **Dermatology Life Quality Index (DLQI)** showed significant improvement over the study period, with scores decreasing from a mean by the third month (P<.001). The DLQI scores can be referenced in Figure 5.

Adverse events were significantly more frequent on the right side compared with the left, as demonstrated in Figure 6. On the right side, 31.6% of patients (18 out of 57) reported adverse events, mainly erythema, burning, and itching. In contrast, on the left side, only 3.5% of patients (2 out of 57) reported adverse events, which were mild burning. This indicates a marked difference in the safety profile of the treatments applied to the 2 sides.

DISCUSSION

Metformin, primarily an anti-diabetic drug, has emerged as a potential treatment for melasma. It has been studied in various clinical trials for inflammatory skin conditions like hidradenitis suppurativa, acanthosis nigricans, psoriasis, acne, and allergic contact dermatitis, showing promising outcomes. In melasma, metformin reduces cAMP levels, which helps lower melanin production in melanocytes by inhibiting key pathways.[6] This drug has been shown to inhibit the energy-sensitive AMP-activated protein kinase (AMPK)-mammalian target of rapamycin signaling pathway that leads to reduced protein synthesis and cell proliferation. As it was recently shown that metformin decreases the cAMP level and that cAMP has a crucial role in melanin synthesis and skin pigmentation, we investigated the effect of metformin on hypopigmentation in vivo.[7]

In our split-face study, the mean Hemi-MASI scores decreased significantly over 3 months, with a reduction of 60.53 ± 15.65% using Kligman's formula and 53.33 ± 14.88% with topical metformin. Similarly, AboAlsoud ES reported MASI score reductions of 56.50% ± 19.44 and 55.97% ± 16.77 in the 2 groups treated with triple combination cream and metformin after 8 weeks.[8] In a study by El-Komy MH, metformin demonstrated superior efficacy compared with placebo, achieving a 68% reduction in MASI scores as compared with 20% with placebo.[9] Even 3 months post-treatment, the metformin side retained a 52% improvement while the placebo side showed only 15%. However, our small sample size and 3-month follow-up duration limited our ability to evaluate a long-term efficacy and safety profile. Although the split-face method was practicable for comparing treatments, it did not fully show the outcomes of full-face treatments. All types of melasma (epidermal, dermal, and mixed) were included, which may have influenced treatment outcomes due to the variations in the responsiveness between these types.

A meta-analysis by Pajaree showed that 15% topical metformin led to a significant reduction of 15% in the MASI score compared with placebo.[10] However, 30% topical metformin showed similar efficacy to the triple combination cream, with a reduction of 3.52% in the MASI score after 8 weeks. The study by Mapar compared metformin with a placebo for a period of 3 months, with metformin showing a greater percentage reduction (17.77%) compared with the placebo (8.02%).[11] A similar percentage reduction of 17.39 was observed by Doaa Abd Elhameed Atta Shokier when treated with metformin for a duration of 3 months.[3] These studies demonstrated the superiority of metformin over the placebo. However, when compared with other treatments such as Kligman's formula and the triple combination cream (TCC), improvements achieved with metformin were not as significant, which was concordant with our study results.

This may suggest that while metformin may show significant results, the other treatment options may provide more distinguished effects in treating melasma.

A local study done in Lahore Pakistan compared the effect of 4% hydroquinone with metformin in 2 groups of patients with epidermal melasma.[12] Group A treated with metformin showed a greater mean percentage reduction in the MASI score (60.28 ± 14.04) as compared with Group B treated with 4% hydroquinone (55.02 ± 13.35). This difference with our study may be attributed to the fact that this study assessed full-face treatment effects as compared with our study, where the split-face method evaluated

only localized treatment effects. Also, our study included all melasma types, which may have affected the results due to the differences in the responsiveness towards treatment between dermal, epidermal, and mixed melasma.

The study by Nermeen Samy Abdel Fattah et al also employed the split-face method to compare the effects of 30% metformin solution with tranexamic acid solution.[13] However, they used micro-needling as an adjunct to topical treatments, enhancing drug penetration and thus increasing the efficacy. While not statistically insignificant, the percentage change of hemi-MASI score was more pronounced with TXA treatment compared with Metformin treatment, which was in agreement with our study; whereas Kligman's formula showed a greater percentage reduction in hemi-MASI scores when compared with Metformin.

In terms of improvement in the PGA scale, our study revealed that Kligman's formula achieved higher levels of improvement, where the percentage of patients with excellent improvement rose from 8.8% to 15.8% and those with good improvement from 14.0% to 61.4%. On the left side, treated with metformin, patients with good improvement increased from 15.8% to 49.1%. Similarly, a study by Doaa Abd Elhameed Atta Shokier observed significant improvement with metformin over time, with 83.3% of patients showing mild to moderate improvement by the second month, which remained constant post-treatment.[3] Channakeshavaiah and Chandrappa showed more balanced results, where 50% of patients in the metformin group and 40% in the TCC group observed mild improvements, whereas a slightly higher percentage of patients showed moderate improvement in the TCC group. This was consistent with our findings where patients treated with Kligman's formula showed a relatively higher degree of improvement.[4]

In agreement with our study, AboAlsoud ES also found significant correlations between melasma improvement grades and decreases in MASI in both the groups treated with metformin and the Triple combination cream.[8]

While comparing the satisfaction rates across different studies, our study showed increased satisfaction from 12.3% to 68.4% with Kligman's formula, and an increase in satisfaction from 12.3% to 47.4% on the side treated with metformin. AboAlsoud ES's study showed moderate improvements compared with our findings, with 50% of patients satisfied and 10% very satisfied.[8] Doaa Abd Elhameed Atta Shokier's study revealed far lower satisfaction, where only 20% were satisfied and 16.7% were unsatisfied.[3] In the Mapar MA study, the metformin group had a greater satisfaction rate (3.66 out of 5) when compared with the placebo group (1.06).[11]

In our study, 18 patients (31.6%) showed adverse events with Kligman's formula as compared with only 2 patients (3.5%) with metformin. Similarly, no adverse effects of metformin application were noted in other studies by Doaa Abd Elhameed Atta Shokier, Channakeshavaiah and Chandrappa, and Aboalsoud ES et al.[3,4,8] This variation may be due to the differences in the patient population, formulation of the topical metformin, and duration of the study.

Our study also observed the DLQI at baseline and at month 3, which showed a significant improvement by month 3. Similarly, another study by Sahar A. Ismail observed the statistically significant decrease in the Melasma Impact Quality of Life Scale (MELASQOL) and MASI scores in the group treated with 1000 mg of systemic metformin in conjunction with Trichloroacetic acid (TCA) peeling.[14] Although our findings suggested an overall improvement in the quality of life, further research focusing on melasma with systemic metformin would be required to establish its efficacy as a mainstay treatment option.

CONCLUSION

Our study showed the efficacy of Kligman's formula in achieving higher improvement rates and satisfaction levels compared with topical metformin. However, metformin provides a viable alternative with fewer adverse events and a greater safety profile. Further research with a larger sample size and the use of systemic metformin could help establish its role in melasma treatment.

DISCLOSURES

The authors have no conflicts of interest to declare regarding this study.

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ORIGINAL ARTICLE

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Iron Oxides in Tinted Sunscreen for Hyperpigmentation: A Product Analysis and Literature Review

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ABSTRACT

Background: Hyperpigmentation disproportionately affects skin of color, often exacerbated by visible light (VL) exposure. Photoprotection in these populations remains underused due to the cosmetic incompatibility of sunscreens and the lack of targeted education. Iron oxides have emerged as essential VL blockers in tinted sunscreens for hyperpigmentation management.

Objectives: To evaluate the role of iron oxide in tinted sunscreens for hyperpigmentation and assess commercial sunscreen product labeling regarding iron oxide content.

Methods: A literature review was conducted using PubMed and Google Scholar to assess clinical studies on iron oxide for hyperpigmentation. A product analysis of 37 tinted sunscreens was also performed, including ingredient review and direct manufacturer contact regarding iron oxide content.

Results: Literature supports that iron oxide-containing sunscreens improve VL-induced pigmentation outcomes. Most products (97.3%) did not list iron oxide as an active ingredient, and only 9.6% of responding brands disclosed iron oxide percentages when contacted, with disclosed concentrations ranging from <1.4% to 10.4%. Although 6 brands (19.3%) claimed their product protects against VL, only one brand publicly detailed any specific corresponding testing performed.

Conclusion: Iron oxides enhance VL protection in sunscreens for skin prone to hyperpigmentation. Standardized reporting of iron oxide content and/or measurement of VL protection is essential to guide evidence-based photoprotection.

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INTRODUCTION

Hyperpigmentation and pigmentary disorders are prevalent dermatological concerns that can significantly impact quality of life, particularly in skin of color, as variations in pigmentation are often more noticeable.[1-3] Treatment options typically fall into several categories, including photoprotection, topical and systemic therapies, chemical peels, and laser or light-based procedures. Many of these are not covered by insurance, leading patients to spend significant financial resources and time to treat their hyperpigmentation. Although numerous treatments are available for hyperpigmentation, managing this condition remains a challenge for dermatologists due to variable outcomes, and single-therapy treatment is not reliably effective.[2-4]

Sun exposure significantly contributes to hyperpigmentation, with contributions from both ultraviolet (UV) and visible light (VL) – especially high-energy visible light (HEV) in the blue range of approximately 400 nm to 490 nm, making photoprotection essential for treatment. However, healthcare providers overall recommend sunscreens more frequently to white patients than to those with richly pigmented skin.[4] Lower sunscreen usage among skin of color, particularly vulnerable to pigmentary disorders, suggests the need for focused education and counseling.[3,4] Furthermore, a majority of sunscreen formulations are cosmetically incompatible with darker skin types, leaving a white cast or ashy discoloration, which lowers patients' desire to use these products, and thus decreases photoprotection.[5] Addressing this issue necessitates not only comprehensive education but also ensuring access to resources and photoprotection products designed to meet the specific needs of patients of color.

Recent studies highlight that iron oxide in tinted sunscreens provides substantial protection against persistent and worsening VL-induced hyperpigmentation in patients of color.[6] However, most tinted sunscreen products do not specify the

percentage of iron oxide or list it as an active ingredient. Iron oxides are pigments and are classified into 3 types: red iron oxide (Fe_2O_3), yellow iron oxide ($Fe(OH)_3$/FeOOH), and black iron oxide (Fe_3O_4). Each type has different peak wavelengths and varying abilities to attenuate visible light.[7-9] The type(s) and proportion of iron oxides are generally not reported, as this is often considered proprietary information. There is no standardized equivalent to SPF for VL attenuation. Few companies or studies report metrics such as the percentage of VL blocked. Tinted sunscreens, especially zinc-based with iron oxides, can have HEV protection; zinc alone provides some attenuation in the 400-450 nm range of HEV and works synergistically with iron oxide.[7] Gaining a deeper understanding of iron oxides and VL protection can empower dermatologists to recommend more effective products for skin of color and manage this dermatological concern.

This literature review aims to examine the role of iron oxide in mitigating hyperpigmentation. Tinted sunscreens identified as compatible with skin of color were also analyzed to determine whether iron oxides were reported among their listed ingredients. This study seeks to highlight the importance of iron oxide in tinted sunscreens and advocates for the consideration of standardization of reporting or measurement of VL protection to promote informed consumer choices and outcomes.

MATERIALS AND METHODS

Literature Review

A comprehensive search of Google Scholar and PubMed related to iron oxides and hyperpigmentation was performed. Search terms and keywords included: "iron oxides", "ferrous oxide", "ferric oxide", "sunscreen," "hyperpigmentation," "tinted sunscreen, "mineral sunscreen," "visible light," "ultraviolet," "melasma," and "skin of color." Publications were considered eligible if they were published in English and included original clinical research, clinical trials, systematic reviews, meta-analyses, or expert consensus guidelines. Studies were included based on their relevance to the clinical utility and efficacy of iron oxides in sunscreens for the management of hyperpigmentation.

Product Analysis

Tinted sunscreen product analysis was performed as an epidemiologic assessment of commercially available products. A list was compiled from a Google search with terms including "tinted SPF," "tinted sunscreen," "sunscreen for skin of color," "sunscreen for darker skin tones," "sunscreens for hyperpigmentation," and "sunscreens that don't leave a cast." These included products recommended by prominent beauty/health sources including *Cosmopolitan, Oprah Daily, InStyle, Women's Health Mag, Vogue*, CNN, and dermatologist-recommended products from blog posts and social media from August 2024 to June 2025, and a 2020 article from the *International Journal of Women's Dermatology*.[10] Non-tinted sunscreens were excluded from review, and only products marketed or labeled as "tinted" were included. Consumer reviews of the tinted sunscreens identified from the above sources were searched for comments on skin of color, no white cast, or other favorable characteristics prior to selection. Ingredient lists were analyzed to determine if iron oxides or information about visible light protection testing were reported. In addition, companies were contacted through email or online submission form listed on their websites, or through local representatives, to inquire about the percentage of iron oxides. Descriptive statistics were performed in Excel.

RESULTS

Literature Review

While UV filters such as zinc oxide and titanium dioxide effectively protect against UVA and UVB radiation, their ability to shield the skin from VL remains limited. In contrast, iron oxide pigments provide an additional layer of protection against VL, which has been especially implicated in the exacerbation of hyperpigmentation disorders.[2,3]

Iron oxide pigments have emerged as a valuable addition to sunscreen formulations due to their unique ability to attenuate VL. A comparative study evaluated 2 sunscreen formulations containing 4.87% and 27.25% iron oxide against a mineral SPF 50+ sunscreen composed solely of zinc oxide and titanium dioxide in individuals with Fitzpatrick skin phototypes greater than type III.[3] The results indicated that the iron oxide-containing formulations were significantly more effective in improving pigmentation, underscoring the clinical benefit of incorporating VL blockers in sunscreens for patients with hyperpigmentation. Further supporting the photoprotective role of iron oxides, another study in 2021 examined formulations containing red, yellow, and black iron oxides along with patented skincare ingredients.[7] Using diffuse transmittance spectroscopy, these formulations demonstrated 71.9% to 85.6% attenuation or blockage of HEV in the 415 nm to 465 nm range (blue light).[7] The findings suggest that iron oxides, particularly when combined with zinc oxide, enhance blue light protection and may offer a promising defense against HEV exposure.

The clinical relevance of this enhanced protection is further illustrated in a study conducted in 2014, which assessed the efficacy of HEV protective sunscreen in the treatment of melasma. In this 8-week trial, 61 participants undergoing treatment with hydroquinone were randomized to receive either a UV-only sunscreen or a UV + HEV sunscreen containing iron oxides.[11,12] The UV + HEV group exhibited a significantly greater reduction in Melasma Area and Severity Index (MASI) scores (75% vs. 60%; $P<0.001$), along with improvements in skin lightness and melanin content.[11,12] These findings reinforce the therapeutic value of iron oxide-containing sunscreens in managing pigmentary disorders.

Recent studies have focused on improving our understanding of how efficacy varies across different formulations. A 2023 study evaluated the protective effects of 4 different sunscreen formulations against skin changes induced by VL and UVA1 in 12 participants with Fitzpatrick skin types III to IV.[13] The sunscreens were applied to specific areas on the participants' backs, which were then exposed to VL + UVA1. Erythema and pigmentation were subsequently measured using investigator global assessment, colorimetry, and diffuse reflectance spectroscopy. Formulations containing 1% and 4% iron oxides demonstrated significantly better protection than those lacking iron oxides.[13] Notably, the formulation containing 1% iron oxides, along with titanium dioxide and antioxidants, provided the most consistent and effective defense against both erythema and pigmentation, outperforming even the product with a higher concentration of iron oxides.[13] These findings suggest that photoprotective efficacy may depend not only on the concentration of iron oxides, but also on the proportions of different iron oxides, as well as combined effects of additional active ingredients. Further studies are needed to clarify the relationship between iron oxide concentration, proportions, and clinical protection.

A study conducted in 2024 investigated the current counseling practices of dermatology practitioners (board-certified dermatologists, residents, fellows, nurse practitioners, and physician assistants) regarding VL protection to their patients.[14] Of the 974 respondents, the majority (91.68%) reported actively counseling patients on VL protection, especially for hyperpigmentation (70.92%). However, only 10.34% of those who provided such counseling specifically recommended sunscreens with ingredients addressing VL protection – such as iron oxides and antioxidants – for melanin-rich skin; while almost half (48.89%) recommended such sunscreens for management of melasma or post-inflammatory hyperpigmentation. Of the 8.32% who reported not counseling their patients on VL protection, the primary reasons were an absence of standardized guidelines (50.62%), difficulties in recommending appropriately tinted sunscreens (27.16%), and limited availability of sunscreen options (23.46%).[14] This study further emphasizes the clinical importance of iron oxide visibility and standardized reporting of VL protection for tinted sunscreens to guide clinical practices.

Most recently, a 2025 study was conducted to evaluate the benefits of incorporating iron oxides into sunscreen formulations for patients with photodamage and melasma.[15] This 12-week study compared the effects of SPF 50 sunscreen alone vs SPF 50 with iron oxides in healthy women with Fitzpatrick skin types III to VI.[15] Colorimetric measurements were performed, and clinical evaluations revealed that both sunscreen formulations improved overall skin quality. However, the addition of iron oxides led to early improvement over baseline in skin texture and appearance in both photodamage and melasma subgroups.[15] The benefits were most pronounced in the melasma subgroup, where 36% of participants using SPF 50 with iron oxides showed superior improvement in skin radiance compared with 0% in the SPF 50 only group.[15] These clinical findings highlight the importance of VL protection and support the integration of iron oxide formulations into daily photoprotection routines to address indoor and outdoor light exposure.

Product Analysis

Thirty-seven tinted sunscreens were identified from a total of 31 brands, some brands having multiple products. 100% of brands did not report the percentage of iron oxides publicly, and 97.3% did not report iron oxide as an active ingredient on publicly available product information online. Six brands (19.3%) included a claim that the product prevents against VL, blue light, or HEV light; however, only one brand (3.2%) noted and described any specific corresponding testing performed.[16] Of the 24 brands that responded when contacted (77.4% response rate), only 3 brands (9.6%) disclosed the percentage of iron oxide, which ranged from <1.4% to 10.4%. The remaining 90.3% declined to provide this information, citing proprietary formulation details or internal policy.

DISCUSSION

Collectively, these studies highlight the growing importance of iron oxide pigments in modern sunscreen development. Their inclusion not only enhances protection against VL but also offers therapeutic and preventive benefits for individuals prone to hyperpigmentation. However, further research is warranted to elucidate the optimal concentration and formulation strategies that maximize clinical efficacy across diverse skin types and pigmentary conditions. One limitation to our understanding of VL blockers in melanin-rich skin is our lack of universal terminology to describe and categorize skin pigmentation.[17-20]

While current evidence supports the role of iron oxides in reducing hyperpigmentation, sunscreen products queried do not publicly disclose the percentage of iron oxide used, limiting patients' ability to make informed decisions. Given that iron oxide contributes to protection against VL, a known trigger for hyperpigmentation, there is a strong rationale for listing it as an active ingredient in tinted sunscreens. Transparency around iron oxide concentrations would not only benefit patients and providers but could also encourage standardization across the industry.

Disclosing the percentage and/or ratios of iron oxides is unlikely to compromise proprietary formulations, as the majority of the sunscreens' composition would remain undisclosed. Although there is a lack of data identifying the exact concentration of iron oxide needed for clinical effectiveness, existing studies consistently support its benefit in pigmentary disorders. Future research should aim to determine optimal dosing thresholds, while manufacturers should be encouraged to report iron oxide content to support evidence-based skincare.

Safety and Tolerability

Topical use of iron oxides in sunscreens is generally safe and well-tolerated, with no reports of adverse events identified in the reviewed literature. Very rarely, allergic contact dermatitis to topical iron oxide used in cosmetics has been reported; only 2 reports were identified in a literature search specifically for adverse effects, and both involved a reaction to mascara.[21-22]

CONCLUSION

Given the current lack of sufficient reporting of VL attenuating ingredients, patients with hyperpigmentation should look for a sunscreen with zinc oxide and iron oxides, even if the details of iron oxides are not reported. Iron oxides are not UV filters, so they are not recognized by the FDA as a photoprotective active ingredient. However, if a product claims to protect against visible light, iron oxides should be considered as an active ingredient for this purpose – ideally with the percentage(s) listed – and visible light protection testing should be reported. We encourage the cosmeceutical industry to consider increased and eventually standardized reporting of iron oxides and tested VL protection to best help patients with hyperpigmentation choose optimal photoprotection.

DISCLOSURES

All authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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The Emerging Role of Metformin in Skin Cancer: Mechanistic and Clinical Insights

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ABSTRACT

Background: Metformin, widely used for type 2 diabetes mellitus, has demonstrated antitumor effects through modulation of metabolic and immune pathways. This review explores its potential role in the prevention and treatment of skin cancers, including melanoma and nonmelanoma skin cancers (NMSCs).

Methods: A structured PubMed search was conducted in April 2025 to identify English-language, peer-reviewed original research articles evaluating the effects of metformin on melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Experimental, observational, and clinical studies were included; reviews and meta-analyses were excluded.

Results: Twenty studies met the inclusion criteria. In melanoma models, metformin inhibited tumor proliferation, suppressed epithelial-mesenchymal transition, and enhanced immune responses. Observational studies reported improved recurrence-free survival and treatment outcomes, although findings were inconsistent. In NMSC studies, metformin use was associated with reduced incidence of BCC and SCC. Preclinical models demonstrated delayed tumor development and an enhanced response to photodynamic therapy following metformin treatment.

Discussion: Mechanistic and preclinical data support a biologically plausible role for metformin in skin cancer prevention and therapy. Evidence is strongest for BCC, particularly in enhancing photodynamic therapy and reducing incidence in at-risk populations. Melanoma studies suggest synergy with immunotherapy, but clinical results remain variable.

Conclusion: Metformin shows promise as a low-cost, well-tolerated adjunctive therapy in dermatologic oncology. Further prospective and controlled studies are needed to clarify its efficacy, optimize dosing, and identify populations most likely to benefit.

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INTRODUCTION

Metformin, a first-line treatment for type 2 diabetes mellitus (T2DM), is increasingly recognized for its potential therapeutic relevance in dermatologic oncology. Beyond its effects on glycemic control, metformin modulates several key biologic pathways implicated in tumor development, including the activation of AMP-activated protein kinase (AMPK), inhibition of oxidative phosphorylation, reduction of oxidative stress, and suppression of proinflammatory and proliferative pathways. These mechanisms overlap with key drivers of cutaneous carcinogenesis, such as metabolic reprogramming, chronic inflammation, and immune evasion.[1,2]

As a result, metformin has garnered attention for its potential role in the prevention and treatment of both melanoma and nonmelanoma skin cancers (NMSCs). In basal cell carcinoma (BCC), early evidence suggests that metformin may enhance the efficacy of photodynamic therapy and reduce tumor risk. In melanoma, metformin has been shown to inhibit epithelial-mesenchymal transition and augment antitumor immune responses. By enhancing the effects of immune checkpoint inhibitors, such as PD-1 blockade, metformin may contribute to improved treatment outcomes.[3]

This review explores the emerging evidence supporting metformin's role in skin cancer prevention and management, with a focus on mechanistic pathways and context-specific clinical applications.

MATERIALS AND METHODS

In April 2025, a structured literature review was conducted using PubMed to evaluate the effects of metformin on skin cancers, including melanoma and NMSCs. The search strategy employed combinations of the keyword "metformin" with terms such as "skin cancer," "melanoma," "basal cell carcinoma," "squamous cell carcinoma," and "nonmelanoma skin cancer." Eligible

studies were limited to English-language, peer-reviewed original research articles, including experimental studies, observational studies, and clinical case reports. Review articles, editorials, and meta-analyses were excluded.

For each included study, data were extracted on study design, country of origin, population or experimental model, metformin dose and duration, route of administration, follow-up period, and primary outcomes. Three researchers independently reviewed and extracted the data, with discrepancies resolved by consensus. Results were categorized by cancer subtype and type of study to highlight mechanistic insights and therapeutic findings relevant to metformin's role in skin cancer.

RESULTS

A total of 20 studies met the inclusion criteria and were thus included in this review. These encompassed experimental models and clinical studies evaluating metformin's effects in melanoma and NMSCs, primarily BCC and squamous cell carcinoma (SCC).

Among melanoma-focused studies (Table 1), experimental models reported decreased melanoma cell proliferation, inhibition of epithelial-mesenchymal transition, and changes in immune-related pathways following metformin treatment. Clinical studies included cohort analyses and retrospective case series evaluating recurrence-free survival and treatment outcomes among patients with melanoma who used metformin. In NMSC studies (Table 2), the use of metformin was associated with lower incidence rates of BCC and SCC in several observational studies. Preclinical studies in murine models demonstrated delayed tumor development and reduced lesion size with both oral and topical administration of metformin. Some studies also evaluated the combination of metformin with photodynamic therapy or other topical agents.

Full study characteristics, including study design, cancer subtype, dosage, administration route, and primary outcomes, are detailed in Table 1 (melanoma) and Table 2 (NMSCs).

DISCUSSION

Research suggests that metformin may offer context-specific benefits in skin cancer, with emerging support for a chemopreventive role in BCC and potential synergy with immunotherapy in melanoma. An observational study of 40,235 individuals, including many with type 2 diabetes mellitus, reported a reduced incidence of BCC among metformin users, with a multivariable-adjusted odds ratio of 0.33, indicating a 67% reduced odds compared with nonusers. The study observed that the risk reduction appeared more pronounced for BCC than for SCC; however, the study was not designed to formally compare subtypes.[4] Although a separate investigation examining NMSC recurrence found no significant association with metformin use, the broader clinical evidence continues to support a potential role in NMSC prevention.[17,20]

Although BCC is typically indolent, resistant tumors may exhibit metabolic vulnerabilities that can be therapeutically targeted. Metformin has been shown to enhance the efficacy of photodynamic therapy in BCC by activating AMPK and inhibiting oxidative phosphorylation. Similar metabolic suppression has also demonstrated antitumor effects in patient-derived cells and mouse models of aggressive SCC.[18,21] However, further comparative studies are warranted to determine whether metformin's effects differ meaningfully between skin cancer subtypes.

Preclinical models provide additional support for metformin's antitumor activity. In obese murine models, metformin inhibited SCC development and reduced epidermal hyperplasia in a dose-dependent manner, suggesting its potential to modulate tumor-promoting metabolic environments.[16] While clinical evidence in SCC is more limited, preclinical models such as those by Welponer et al have shown that metformin can suppress both oxidative phosphorylation and glycolysis in aggressive cutaneous SCC, resulting in reduced tumor viability. These findings support the possibility that SCC and BCC may exhibit distinct metabolic dependencies. In addition, in vitro studies of vismodegib-resistant BCC cell lines have shown enhanced sensitivity to photodynamic therapy and decreased cell viability following metformin treatment.[17] These mechanistic insights may explain the lower BCC incidence observed in some clinical studies and reinforce the need to further investigate metformin's potential in skin cancer prevention, particularly in patients with metabolic dysfunction or elevated cancer risk.

In melanoma, the mechanistic data are compelling, although clinical findings remain variable. Preclinical research has demonstrated that metformin inhibits epithelial-mesenchymal transition, suppresses metastasis, and activates tumor-suppressive pathways, including AMPK and p53.[5,21] These findings support its use in combination with immune checkpoint inhibitors. In a multi-institutional retrospective cohort study of 668 diabetic melanoma patients, metformin use was associated with significantly improved five-year recurrence-free survival in early-stage disease, with recurrence rates of 32.3% vs 47.7% in stage I/II patients and 58.3% vs 77.3% in stage III patients, compared with those not exposed to metformin[3] Another observational study involving patients with metastatic melanoma receiving checkpoint inhibitors found that those concurrently treated with metformin had higher response and disease control rates, with fewer new metastases.[4] However, these findings have not been consistently replicated. The KEYNOTE-054 phase III trial evaluating adjuvant pembrolizumab in resected high-risk stage III melanoma found no association between metformin use and improved recurrence-free or distant metastasis-free

TABLE 1.

Key Characteristics and Findings of Studies Evaluating Metformin's Role In Melanoma

Authors	Year	Country	Study Design	Setting	Study Population/ Model	Dosage	Route of Administration	Treatment Duration / Follow-Up	Primary Outcome
Afzal et al.[4]	2018	USA	Cohort	Clinical	55 patients (22 on metformin)	Variable (500 mg - 1000 mg twice daily)	Oral	Median: 13.5 months; Until Feb 15, 2018	Patients receiving metformin + immunotherapy showed improved response rates and survival trends compared to immunotherapy alone.
Augustin et al.[3]	2023	USA	Cohort	Clinical	668 patients	Variable (250–2000 mg/day)	Oral	Variable; Patients from 1996–2020	Diabetic melanoma patients on metformin showed significantly better 5-year outcomes than those not on metformin.
Cerezo et al.[5]	2013	France	Experimental	In vitro + in vivo	In vitro: melanoma cell lines In vivo: nude mice injected with 1205 Lu-Luc melanoma cells	In vitro: up to 10 mmol/L In vivo: 60 mg/kg/day	In vitro: directly added to medium In vivo: intraperitoneal injection	In vitro: 24–96 hours (most invasion assays at 24h) In vivo: up to 39 days; In vitro: 24 hours for invasion assays In vivo: Bioluminescence tracked over 39 days	Inhibition of melanoma invasion.
Da Gu et al.[6]	2025	China	Experimental	In vitro + in vivo	In vitro: A375 human melanoma cells In vivo: Female BALB/c-nu mice xenograft model	In Vitro: 20–60 mM In Vivo: 250 mg/kg/day	In Vitro: culture medium In Vivo: oral gavage	In Vitro: 0, 24, 48, 72, 96 hours In Vivo: 12 days; In vitro: 0–96h In vivo: monitored every 3 days for 12 days	Significantly inhibited SKCM proliferation and induced ferroptosis via the ATF3/NRF2 axis.
Kennedy et al.[7]	2023	Multi-national	RCT	Clinical	1019 patients with stage III melanoma (54 used metformin)	Variable	Oral	Defined as use at baseline: from randomisation to 30 days thereafter; Median 42.4 months	Not associated with any significant improvement in recurrence-free survival or treatment efficacy of pembrolizumab in high-risk stage III melanoma.
Krakowski et al.[8]	2023	Sweden	Cohort	Clinical	23,507 patients with melanoma; 1,162 patients with both melanoma and type 2 diabetes	Variable	Oral	Prediagnostic median: 1.4 years; Postdiagnostic median: 2.3 years; Until death or 31 Dec 2017; median 4.1 years	Among melanoma patients with type 2 diabetes, metformin use was associated with improved overall survival.
Lehraiki et al.[9]	2014	France	Experimental	In vitro + in vivo	In vitro: B16-F10 mouse melanoma cells, normal human melanocytes, and human melanoma cell lines In vivo: C57BL/6J mice Ex vivo: reconstructed human epidermis, skin biopsies	In Vitro: 5mM and 10 mM In Vivo: 10 mM Ex Vivo: 10 mM	In Vitro: directly added to medium In Vivo: topical application to tail Ex Vivo: directly added to medium	In Vitro: 2, 24, 48, or 72 hours In Vivo: Daily for 8 weeks Ex Vivo: 15 days; Measured during/immediately post-treatment	Significantly inhibited melanin synthesis in melanoma cells and normal human melanocytes by reducing cAMP accumulation and downregulating key melanogenesis genes.
Ryabaya et al.[10]	2019	Russia	Experimental	In vitro	2D and 3D in vitro melanoma cell cultures (monolayer, spheroids, Matrigel invasion)	1 mM	directly added to medium	24–48 hours; Up to 12 days (colony assay); 2–3 days (invasion assays)	Enhanced the efficacy of binimetinib against melanoma cells by reducing viability.
Suwei et al.[11]	2022	China	Experimental	In vitro + in vivo	In vitro: A2058, G361 In vivo: C57BL/6 mice	In Vitro: 16.61 mM or 15.10 mM In Vitro: 3 mg/kg	In Vitro: directly added to medium In Vitro: Intraperitoneal injection	In Vivo: 14 days or 7 days before and 14 days after injection In Vitro: 48 hours; In Vivo: 2 weeks post-injection In Vitro: Observed over 48 hours	Inhibited melanoma cell metastasis by suppressing epithelial-mesenchymal transition (EMT) and downregulating miR-5100/SPINK5/ STAT3 signaling.
Tomic et al.12	2011	France	Experimental	In vitro + in vivo	In vitro: A375, SKMel28, WM9, G361 In vivo: Nude mice, C57BL/6 mice	In Vitro: 5–10 mM In Vivo: 2 mg/ mouse/day	In Vitro: directly added to medium In Vivo: oral	In Vitro/Ex Vivo: 24–96 hours In Vivo: 3 weeks; In Vitro: During and at end of treatment period In Vivo: Through and at end of study	Significantly inhibited melanoma tumor growth and prolonged remission via dual mechanisms of autophagy induction and apoptosis.
Tsai et al.[13]	2024	Taiwan	Experimental	In vitro + in vivo	In vitro: Human melanoma cell lines (A2058, A375, MeWo) In vivo: Human melanoma tissue samples	5 mM	directly added to medium	4 days; In vivo cohort: Up to ~29 years (retrospective clinical samples from 1990–2019)	Downregulation of LINC00094 inhibited melanoma proliferation, migration, invasion.
Tseng et al.[14]	2019	Taiwan	Experimental	Clinical	A2058 and A375 melanoma cells	1, 5, and 10 mM	directly added to medium	3 days; Measured during/immediately post-treatment	Significantly suppressed melanoma cell growth and motility by inducing G2/M phase cell cycle arrest and apoptosis.

Abbreviations: BALB (Bagg albino immunodeficient mouse strain), EMT (epithelial-mesenchymal transition), RCT (randomized controlled trial), SKCM (skin cutaneous melanoma), USA (United States of America)

TABLE 2.

Key Characteristics and Findings of Studies Evaluating Metformin's Role In Nonmelanoma Skin Cancer

Authors	Year	Country	Study Design	Setting	Study Population/ Model	Dosage	Route of Administration	Treatment Duration / Follow-Up	Primary Outcome
Adalsteinsson et al.[15]	2021	Iceland	Case-control	Clinical	6,880 skin cancer cases (first-ever BCC, SCC in situ, or invasive SCC) and 69,620 matched population controls	Stratified by DDU: 1–500, 501–1500, >1500	Oral	Metformin exposure assessed prior to cancer diagnosis (2003–2017 data); 15 years (2003–2017)	Associated with a significantly lower risk of developing BCC. No effect on SCC.
Checkley et al.[16]	2014	USA	Experimental	Clinical	FVB/N female mice	50–250 mg/kg/day	Oral	2 to 43 weeks (depending on experiment; longest was tumor promotion study); Up to 49 weeks	Inhibited development of SCC and papilloma size in obese mice treated with metformin in a dose-dependent manner.
Haq et al.[17]	2024	USA	Case-control	Clinical	SCC Cases: 4,111, SCC Controls: 16,444; BCC Cases: 8,047, BCC Controls: 32,188	Ever use vs. never use	Oral	Minimum 2 years exposure before SCC/BCC diagnosis; Not specified explicitly (retrospective database analysis)	Associated with a significantly lower risk of both SCC and BCC.
Mascaraque et al.[18]	2020	Spain	Experimental	In vitro + in vivo	In vitro: Murine basal cell carcinoma (ASZ and CSZ cell lines) In vivo: Nude mice	In vitro: 75 µM In vivo: 200 µg/mL in drinking water	In vitro: directly added to medium In vivo: oral via drinking water	24 h Metformin pretreatment before PDT; In vivo: tumor volume monitored over 15 days	Metformin enhanced PDT cytotoxicity, induced G0/G1 arrest, activated AMPK, and reduced glycolysis
Mousa et al.[19]	2022	Egypt	Experimental	Clinical	Chemically induced skin cancer in mice (DMBA model)	1.7% w/w in ethosomal gel	Topical	4 weeks; Weekly for 28 days	Ethosomal metformin gel improved anti-tumor activity, skin penetration, and drug retention over control.
Ravishankar et al.[20]	2020	USA	Cohort	Clinical	174 patients (117 nondiabetics, 20 diabetics on metformin, 37 diabetics not on metformin)	Varied (<1,000 mg to >2,000 mg daily)/Typical clinical doses (under 2000 mg/day)	Oral	Not standardized, based on usage at time of first NMSC; 3 years	No significant reduction in risk of recurrent NMSC in diabetics on metformin.
Welponer et al.[21]	2023	Austria	Experimental	In vitro + in vivo	In vitro: RDEB-SCC cell lines (human) In vivo: C3H mouse model (SCC-VII tumor line) In silico: Microarray and gene signature analyses (GSE130925, GSE11357)	In vitro: 0–10 mM (optimal effect at 10 mM) In vivo: 5 mg/mL in drinking water (~30 mM)	In vitro: directly added to medium In vivo: oral	In vitro: 24–72 h (short-term), 2 weeks (long-term) In vivo: ~5 weeks (up to endpoint or tumor volume >500 mm^3); In vivo: 35 days maximum or until tumor reached 500 mm^3	Reduced cell viability and clonogenic potential in vitro, and delayed tumor growth and improved survival in a murine model of aggressive cSCC.
Zhou et al.[22]	2021	Multi-national	Experimental	In vitro + in vivo	In vitro: primary human and mouse keratinocytes, reconstituted human skin model In vivo: DMBA/TPA-induced mouse model	In vitro: phenformin 1 mM In vivo: phenformin 100 mg/kg/day	In vitro: directly added to medium In vivo: intragastric (mouse), intraperitoneal (reconstituted model)	In vitro: 2 weeks (reconstituted skin), 24–72h (cell assays) In vivo: 9 weeks; In vivo: up to 25 weeks	Suppressed tumor growth and enhanced keratinocyte differentiation.

Abbreviations: AMPK (AMP-activated protein kinase), ASZ (ASZ001 murine basal cell carcinoma cell line), BCC (basal cell carcinoma), DDU (defined daily use), DMBA (7,12-dimethylbenz[a]anthracene), FVB/N (Friend Virus B-type mouse strain), NMSC (nonmelanoma skin cancer), PDT (photodynamic therapy), RDEB (recessive dystrophic epidermolysis bullosa), SCC (squamous cell carcinoma), TPA (12-O-tetradecanoylphorbol-13-acetate), USA (United States of America)

survival, nor any modification of pembrolizumab efficacy.[7] Similarly, a national cohort study found no survival benefit linked to metformin use in diabetic melanoma patients.[8]

Several limitations affect the interpretation of current evidence, including heterogeneity in metformin dosing, tumor stage, treatment duration, and patient metabolic profile. Additionally, most of the clinical studies reviewed were observational, limiting causal inference. Unlike therapies that act directly on tumor-specific mutations, metformin modulates host-level immunometabolic pathways, which may lead to context-dependent responses. Moreover, few randomized trials have been specifically designed to evaluate metformin's efficacy in skin cancer, limiting the strength of existing conclusions.

Given the increasing incidence of skin cancer and the limitations of existing therapeutic strategies, particularly for high-risk or metabolically dysregulated populations, metformin represents a promising candidate for therapeutic repurposing. Its favorable safety profile and known effects on systemic metabolism and immune regulation support further exploration in dermatologic oncology.[22] Clarifying its context-specific activity across skin cancer subtypes and determining how mechanistic pathways translate into clinical benefit remain important areas for future research.

CONCLUSION

Beyond its role in type 2 diabetes mellitus, metformin has emerged as a potential adjunct therapy in the prevention and treatment of skin cancer. Evidence from preclinical and observational studies suggests beneficial effects in both melanoma and nonmelanoma skin cancers, including tumor suppression, metabolic modulation, and enhanced treatment response. Given its accessibility, safety, and biologic plausibility, metformin warrants continued investigation in prospective, controlled studies to clarify its role in dermatologic oncology and identify patient populations most likely to benefit.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

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Weight Loss and Its Impact on Soft Tissue

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ABSTRACT

Background: Rapid and intentional weight loss can result from bariatric surgery, pharmacologic agents such as glucagon-like peptide-1 receptor agonists, and intensive lifestyle changes. Although effective in lowering body weight, these interventions often produce broader physiologic effects. Patients may experience changes beyond size, including decreased skin firmness, muscle loss, and reduced bone density.

Objective: To describe the dermatologic and structural consequences of rapid weight loss and review current and emerging management strategies.

Methods and Materials: A narrative review was conducted using PubMed and Google Scholar to identify English-language literature published between 2000 and 2025 on soft tissue changes associated with rapid weight loss.

Results: Rapid weight loss impacts collagen, elastic fibers, adipose tissue, muscle mass, and skeletal integrity. Management strategies include nutritional optimization, resistance-based physical activity, energy-based devices, biostimulatory injectables, and, in advanced cases, surgical procedures. Regenerative therapies are also under investigation.

Conclusion: As rapid weight loss becomes increasingly common, dermatologists are encountering a broader range of cosmetic and structural concerns. A multidisciplinary, evidence-informed approach is critical for addressing these issues and improving patient outcomes.

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INTRODUCTION

Obesity and metabolic syndrome, commonly known as Syndrome X, have become increasingly common health concerns.[1] As reported by the Centers for Disease Control and Prevention (CDC), nearly three-quarters of American adults are currently classified as obese or severely obese.[2,3] Recently, glucagon-like peptide-1 (GLP-1) agonists, including semaglutide and tirzepatide, have gained popularity as a means of weight loss due to their effectiveness in controlling blood sugar and triggering satiety.[4]

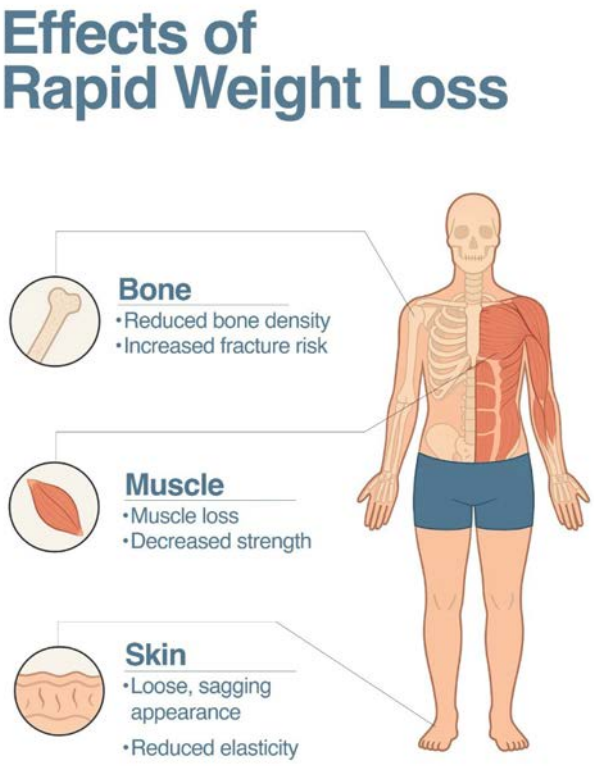
The increasing use of GLP-1 agonists has raised concerns among physicians, non-physician providers, and patients regarding potential side effects. Skin-related issues, notably increased skin laxity and muscle loss, are often linked directly to these medications.[5] However, attributing these skin changes exclusively to GLP-1 agonists might neglect other physiological factors associated with rapid weight loss. Several studies have documented that substantial weight loss, irrespective of the approach used, leads to noticeable changes in body composition, affecting fat stores, muscle health, and skin elasticity.[6,7] Research comparing bariatric surgery, lifestyle interventions, and GLP-1 therapies consistently finds similar outcomes in tissue composition.[8,9] These findings suggest that tissue changes are not solely a result of the medication itself but reflect a broader physiological response to rapid weight reduction, involving caloric restriction, hormonal shifts, and the pace at which fat and lean mass are lost.

This manuscript addresses the influence of rapid weight loss on body tissues, separating these general effects from those specifically caused by GLP-1 agonists. Recognizing substantial weight reduction as a major contributor to these changes can help dermatologists adopt comprehensive strategies for patient care. As GLP-1 agonists potentially gain approval for treating additional conditions such as alcoholism, obstructive sleep apnea, depression, and Alzheimer's disease, dermatologists will need to consider and manage a broader range of skin-related issues associated with these treatments.[10]

MATERIALS AND METHODS

A narrative review was conducted to evaluate the dermatologic and structural consequences of rapid weight loss. Literature was identified through PubMed and Google Scholar searches for English-language articles published between 2000 and 2025. Keywords included "GLP-1 receptor agonists," "bariatric surgery," "skin laxity," "soft tissue changes," and "dermatologic management." Reference lists of key publications were manually screened to identify additional relevant studies.

FIGURE 1. Rapid weight loss can reduce skin elasticity, cause muscle loss and weakness, and decrease bone density, increasing fracture risk.



RESULTS

Rapid weight loss refers to losing more than 5% of one's total body weight within 6 months.[11] This weight reduction can occur intentionally, through medical treatments and lifestyle modifications, or unintentionally as a symptom of underlying health conditions. Procedures like bariatric surgery, which limit stomach size or change nutrient absorption, commonly target severe obesity and associated conditions such as type II diabetes mellitus or metabolic syndrome X.[12] Pharmacological treatments like GLP-1 agonists, such as semaglutide and tirzepatide, have gained attention for their ability to control appetite, slow gut motility, manage blood sugar, and promote weight loss.[4] Lifestyle changes involving diet restriction and increased exercise can also produce rapid weight loss, although maintaining such changes can be challenging.[13] Rapid weight loss affects various bodily systems, including metabolism, muscle mass, bone density, and skin elasticity, emphasizing the need for careful management, particularly as GLP-1 agonists become relevant to additional therapeutic uses beyond traditional metabolic conditions (Figure 1).

Clinicians have also observed facial thinning and signs of early aging in individuals who regularly engage in long-distance running or cycling.[14] These changes may be related to reductions in facial fat and possible mechanical strain on soft tissue structures. While few studies have focused on facial features specifically, long-term endurance training has been shown to reduce subcutaneous fat across the body, which may contribute to visible volume loss in the face.[14]

Rapid weight loss influences the skin's structure and function.[15] A sudden decrease in body weight can affect collagen and elastin, which will affect the skin's firmness and flexibility.[16] The skin is unable to properly retract during rapid weight loss, which often appears as sagging and wrinkles.[16] On a cellular level, histologic studies have shown that massive weight loss can lead to disorganization of collagen fibers and a reduction in the density of collagen and elastic fibers within the dermis.[16] Fibroblast activity may also decline, impairing the skin's ability to remodel and maintain extracellular matrix integrity.[16] This may also lead to the thinning of the epidermis and possibly the dermis, a condition known as atrophy, which can make the skin appear more fragile and translucent.[15] These histological changes help explain why skin often lacks elasticity and does not respond optimally to surgical contouring procedures after rapid weight loss.

Rapid weight loss affects the deeper fat and muscle compartments beneath the skin. The loss of adipose tissue that occurs during weight loss can lead to a loss of structural support for the skin, contributing further to sagging and an aging appearance.[15] This change affects the aesthetic and mechanical properties of the skin, as well as its insulation and cushioning.[17]

Rapid weight loss can also affect the skeletal system. Weight loss without simultaneous strength training can lead to reduced bone density, which, without proper attention, could develop into osteoporosis.[18] Lower bone density increases susceptibility to fractures and related injuries, creating additional health concerns for individuals losing weight quickly. This decline is thought to result from a combination of reduced mechanical loading on bones due to lower body weight, hormonal shifts, and insufficient intake or absorption of key nutrients such as calcium, vitamin D, and protein, particularly common in patients undergoing bariatric surgery or treated with GLP-1 agonists.[19] Without proper management, rapid weight loss can also result in muscle loss.[19] Muscle loss reduces strength and worsens loose skin by removing structural support. Muscle loss, a process called sarcopenia, can be particularly concerning as it not only affects physical strength, endurance, and quality of life measures but also exacerbates the problem of loose skin by reducing the volume that helps to keep the skin taut.[20] These changes are often tied to shifts in dietary habits. Post-bariatric surgery patients are typically limited to small food volumes, and those on GLP-1

agonists frequently report reduced appetite.[21] If protein intake is inadequate, muscle breakdown may be accelerated. Lifestyle factors may also contribute, as gastrointestinal side effects like nausea may discourage physical activity in some patients.[22]

Addressing these problems effectively involves multiple approaches, particularly for individuals on treatments such as GLP-1 agonists. Recommended actions involve a nutritious diet rich in protein to preserve muscle, consistent resistance exercises to sustain muscle structure, and targeted medical or cosmetic treatments to improve skin firmness and maintain bone density.

Keeping skin healthy during weight loss involves careful attention to diet and daily habits. Eating foods containing protein, omega-3 fats, zinc, and vitamins A, C, and E can help the skin remain firm and flexible by supporting collagen.[23] Oral protein intake and supplementation, generally recommended at a daily minimum dose of 1 g per kg of body weight, can also protect muscle tissue, which tends to decrease during rapid weight loss.[24,25] Using lower amounts of GLP-1 agonist medications alongside thoughtful nutrition might further limit negative effects on the skin and muscles.[26]

Regular strength-building activities like weightlifting help preserve muscle size, giving the skin better structural support.[27] Studies have found that individuals doing strength exercises regularly while restricting calories lose less muscle and maintain more strength compared with those who focus only on dietary adjustments.[28]

In addition to nutrition and exercise, cosmetic treatments such as biostimulatory fillers can improve skin appearance after rapid weight loss. Biostimulants like poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) encourage the skin to produce its own collagen naturally, gradually improving volume and firmness.[29] More recent evidence suggests an adipogenic property to PLLA.[30] These injectable treatments are beneficial for restoring lost fullness in areas such as the face, complementing nutrition and physical activity.

Bringing together balanced dietary habits rich in proteins and essential nutrients, continued, early, and regular muscle-building exercises, behavioral changes, and specific medical procedures offers a well-rounded solution. This combined method helps manage cosmetic concerns effectively and promotes overall health, improved appearance, and greater patient satisfaction during rapid weight reduction.

When patients lose weight rapidly, dermatologists should evaluate skin problems promptly. Minimally invasive options are usually the first step, such as treatments involving fractional lasers, ultrasound, radiofrequency, or biostimulants like PLLA or CaHA.[30–32] These procedures help rebuild collagen, tighten skin, and restore fullness, significantly improving overall appearance.

If loose skin becomes severe enough to affect daily activities, hygiene, or emotional health, patients might benefit from surgical consultation. Commonly used surgeries include abdominoplasty, brachioplasty, thighplasty, and rhytidectomy, all of which effectively remove extra skin.[33] Thoughtful patient evaluation and clear discussions before surgery help achieve successful outcomes. Dermatologists often coordinate with other physicians and non-physician providers to choose the most appropriate treatments and manage patient expectations effectively.

Recent clinical findings indicate that certain less invasive skin treatments can effectively address loose skin after substantial weight loss. One clinical trial tested microwave therapy alongside fractional CO2 laser treatments in women experiencing skin laxity after childbirth.[34] Participants reported firmer skin and a decreased amount of striae distensae after undergoing the procedures.[34] Another study assessing PLLA injections found that patients experienced thicker skin and reported positive satisfaction scores, confirming injectable biostimulatory agents' role in restoring skin volume after weight loss.[35]

Ongoing research is examining different ways to combine less invasive skin therapies to address persistent laxity following significant weight reduction. Clinicians are combining techniques such as fractional lasers, ultrasound methods, microneedling, and biostimulants. Initial outcomes from these studies show noticeable improvement in skin texture, collagen levels, and overall appearance, especially in areas with substantial looseness.[36]

Treatments involving platelet-rich plasma (PRP) are also undergoing research for their potential benefits to skin recovery after weight loss. Early data suggest that PRP therapy can boost fibroblast function and collagen formation, leading to visibly firmer and more elastic skin.[37]

New technologies have emerged to address the underlying muscle loss commonly associated with rapid weight reduction and age-related sarcopenia.[20] High-intensity focused electromagnetic (HIFEM) stimulation, with or without synchronized radiofrequency, has been shown to increase muscle volume by approximately 25 percent in targeted areas, as confirmed by MRI analysis.[38] This not only enhances muscle definition but also contributes to better structural support for overlying skin, making it particularly relevant in the context of post-weight loss body contouring. Studies evaluating gluteal applications have shown measurable gains in muscle thickness and improved aesthetic outcomes.[38,39] These approaches offer a promising adjunct to skin-tightening treatments and should be

considered as part of a comprehensive management strategy for patients experiencing physical and cosmetic changes following significant weight loss.

Continued investigation into these methods will help dermatologists and other medical specialties deliver effective, individualized care for patients dealing with skin laxity related to significant weight loss.

DISCUSSION

As pharmacologic therapies like GLP-1 receptor agonists continue to gain popularity, dermatologists are increasingly managing patients experiencing tissue changes following rapid weight loss. While aesthetic concerns, including skin laxity and facial volume loss, are often directly attributed to these medications, comparative evidence from bariatric surgery and lifestyle interventions indicates that the overall physiological impact of rapid weight reduction, particularly its speed and magnitude, is the primary contributor.[40,41]

Dermal white adipose tissue (dWAT) is gaining attention for its structurally and metabolically distinct fat layer, closely integrated with the dermis. dWAT contributes to dermal thickness, elasticity, and facial volume, and its depletion has been implicated in accelerated skin aging.[42] Preliminary studies suggest GLP-1 signaling may influence dWAT homeostasis independently of overall fat loss, prompting new questions regarding the facial changes observed in patients treated with GLP-1 agonists.[43,44] Further research is needed to clarify the extent and reversibility of dWAT remodeling.

While numerous interventions exist, including nutritional optimization and biostimulatory injectables, there remains limited evidence directly comparing their efficacy or determining the optimal sequencing of these treatments. For example, few prospective studies have explored how early versus delayed interventions impact outcomes specifically in patients undergoing GLP-1 therapy.[45] Additionally, existing literature largely centers around post-bariatric surgery populations, leaving gaps in understanding medication-driven tissue changes.[9]

As metabolic therapies are increasingly prescribed for non-obesity indications, dermatologists may be consulted to address aesthetic sequelae and patient dissatisfaction.

CONCLUSION

Rapid weight loss, whether resulting from surgery, treatments like GLP-1 agonists, or major diet and activity changes, can affect skin appearance, muscle strength, and bone health. Although GLP-1 agonist medications often receive attention for these physical changes, research suggests the rate and total amount of weight loss largely determine these effects rather than the peptide itself. Given rising rates of obesity and related metabolic dysfunction, and as GLP-1 agonists find new medical uses, dermatologists have an opportunity to manage related skin and health concerns. Early skin assessment, combined with nutritional support, regular physical exercise, and less invasive treatments such as fractional lasers, radiofrequency therapy, electromagnetic muscle toning therapy, and biostimulatory injectables have successfully addressed skin looseness and muscle loss. Continued research is needed to determine the best approaches and evaluate new treatment combinations, including regenerative methods. Cooperation between dermatologists, endocrinologists, dietary professionals, and surgeons will be helpful to improve patient care, physical outcomes, and overall satisfaction after significant weight reduction.

DISCLOSURES

Dr. Hooper serves as a consultant, speaker, and investigator for Allergan/AbbVie, Revance, and Galderma Laboratories. Dr. Palm serves as a clinical investigator, consultant, and speaker for Allergan/AbbVie, Galderma, Medytox, Merz, Lumenis, BTL, Alastin, Revision, EltaMD, and Invo Aesthetics. Mr. Fathizadeh reports no relevant conflicts of interest.

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ORIGINAL ARTICLE

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Safety and Efficacy of Aminolevulinic Acid 20% Topical Solution Activated by Blue Light for Facial Cutaneous Squamous Cell Carcinoma In Situ

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ABSTRACT

Background: Squamous cell carcinoma in situ (isSCC) is an early-stage cutaneous malignancy that requires effective treatment to prevent progression to invasive SCC. Aminolevulinic acid photodynamic therapy (ALA-PDT) is a noninvasive treatment that selectively targets neoplastic cells. This study evaluated the effectiveness, safety, and tolerability of ALA-PDT for the treatment of patients with facial isSCC.

Methods: In this single-center, investigator-initiated, open-label study (NCT06159842), adult patients with biopsy-confirmed facial isSCC received 2 treatments with 20% ALA and blue light exposure, administered 28 days (± 3 days) apart. Lesions were excised for histopathological assessment 8 weeks after the second treatment. The primary endpoint was complete histological clearance at the end of treatment (EOT). Secondary outcomes included clinical clearance and tolerability.

Results: A total of 32 patients were enrolled in this study, of whom 30 completed the study. All patients achieved complete histological clearance at EOT. Clinical clearance was observed in all patients prior to excision, with 40% achieving clearance by day 49 and the remainder by day 69. Local skin reactions, including erythema and flaking, were mild and resolved over time. Only 1 patient experienced temporary hyperpigmentation. Pain scores remained low (mean, 2.71/10). Two patients reported adverse events considered unrelated to treatment.

Conclusions: ALA-PDT achieved 100% complete histological and clinical clearance with minimal adverse effects, demonstrating its potential as a safe, effective, and cosmetically favorable alternative to surgical excision for the treatment of facial isSCC. Further studies are needed to assess long-term recurrence rates and broader applications.

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INTRODUCTION

Nonmelanoma skin cancer is the most common form of cancer, with cutaneous squamous cell carcinoma (SCC) accounting for more than 20% of all skin cancers.[1,2] Although historically less prevalent than basal cell carcinoma (BCC), SCC carries a significant risk of metastasis and mortality and a poor prognosis.[3-6] Unfortunately, the incidence of SCC continues to rise, as observed in the Rochester Epidemiology Project conducted by the Mayo Clinic, which reported a 263% increase in the incidence of SCC between studies spanning the years 1976 to 1984 and 2000 to 2010.[7] In fact, recent studies have indicated that in areas of high sun exposure such as South Florida, SCC and its subtypes are significantly more prevalent than BCC.[8,9] Ultraviolet radiation exposure, especially ultraviolet A, is the primary risk factor for developing SCC; other risk factors include advanced age, fair skin, carcinogen exposure, chronic inflammation, and immunosuppression.[10,11] SCC often arises from precancerous lesions, including actinic keratoses (AKs) and SCC in situ (isSCC), also known as Bowen disease.[12] isSCC is a common superficial cutaneous malignancy with a reported rate of progression to invasive SCC of 3% to 5%.[13] Treatment of isSCC is crucial to prevent such progression.

Histopathological examination is the mainstay for the diagnosis of SCC, with certain histological features – such as poor differentiation, tumor depth >2 mm, and perineural invasion – indicating a higher risk for recurrence and metastasis.[11,14] The gold standards for the treatment of SCC are Mohs micrographic surgery (MMS), surgical excision, and radiation therapy (RT). MMS or RT may be indicated for high-risk SCC and SCC located

in the head, neck, or genital region.[15,16] For low-risk SCC or isSCC, standard excision with 4- to 6-mm clinical margins of normal-appearing skin is recommended, as per the 2025 National Comprehensive Cancer Network guidelines.[17]

Nonsurgical treatment options for isSCC include radiation therapy, electrocoagulation, cryosurgery, photodynamic therapy (PDT), and, in some cases, topical chemotherapy. Systemic chemotherapy is reserved for advanced SCC.[14,17]

Cure rates for AKs, isSCC, and invasive SCC vary widely by treatment modality. Clearance rates for AKs range from 24% to 91%, depending on the treatment used.[18-20] For isSCC, surgical excision achieves the highest clearance rate (~100%), with a low recurrence rate.[21] Invasive SCC is primarily treated with surgical excision or MMS, both of which offer >90% clearance and lower recurrence; however, challenges remain with incomplete deep margin resection, limited access to MMS, and surgical morbidity, especially for high-risk, anatomically complex, or cosmetically sensitive tumors.[22,23] There is an unmet need for nonsurgical treatments that can provide durable efficacy in isSCC while preserving cosmetic and functional outcomes, especially for lesions in cosmetically sensitive areas such as the face.

PDT has emerged as an effective and cosmetically favorable treatment for many dermatologic conditions, including AKs, BCC, isSCC, and warts.[20,24-27] It involves the application of a photosensitizing agent, such as aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), which converts to its active form, protoporphyrin IX (PpIX), upon illumination. Activated PpIX generates reactive oxygen species, selectively destroying neoplastic cells.[28,29] For isSCC, PDT results in clearance rates ranging from 48% to 100% depending on the treatment regimen and follow-up period.[31-34]

ALA-PDT using a 20% 5-ALA solution with blue light (LEVULAN® KERASTICK® with BLU-U® Illuminator, Sun Pharmaceutical Industries, Inc.) is approved in the US for the treatment of minimally to moderately thick AKs on the face, scalp, and upper extremities.[35] The purpose of this trial is to evaluate the safety, tolerability, and efficacy of PDT consisting of topical PDT and blue light illumination in patients with isSCC on the face.

MATERIALS AND METHODS

Study Design and Population

This single-center, investigator-initiated, open-label study (NCT06159842) was conducted at the Center for Clinical and Cosmetic Research from August 2023 to September 2024. The study protocol was reviewed and approved by the US Institutional Review Board (IRB; IRB number U.S.IRB2023CCCR/01; approval date, July 30, 2024). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent prior to study initiation.

Adult patients with histologically confirmed facial isSCC were enrolled consecutively in the study to reduce selection bias. Lesions must have been diagnosed and histologically confirmed within 6 months prior to screening. Only lesions measuring 0.4 to 1.3 cm in diameter were included. Lesions with histological features of nodular basal cell carcinoma, superficial basal cell carcinoma, other non-SCC tumors, severe squamous metaplasia, or infiltrative desmoplastic or micronodular growth patterns on biopsy, or a history of recurrence of the target isSCC, were excluded.

Treatment and Assessments

Prior to the application of 20% ALA hydrochloric acid (HCl), lesions were gently abraded using 4 x 4 gauze and wiped with alcohol wipes. Following lesion preparation, 20% ALA HCl was applied topically to the lesion and approximately 5 mm of the surrounding area. The treated area was then occluded with a bandage and incubated for 24 hours, as previously described,[36] during which patients were instructed to keep the treatment area dry and avoid direct sunlight. After the 24-hour incubation period, patients underwent PDT using blue light (BLU-U®) at an irradiance of 10 mW/cm^2, delivering a total fluence of 10 J/cm^2 for 16 minutes and 40 seconds. Each patient received 2 ALA-PDT sessions, administered 28 (± 3) days apart.

Eight weeks after the second treatment, the lesions were surgically excised, sectioned at 1-mm intervals using a "bread-loafing" technique, and stained with hematoxylin and eosin. A board-certified dermatologist, blinded to the clinical outcomes, examined the sections to assess for complete histologic clearance. Lesion size and eventual complete clinical clearance (CC), defined as no clinically visible lesion at the site, were assessed by the investigator at each visit.

Pigmentation changes at the lesion site (hyperpigmentation, hypopigmentation, and depigmentation) were semi-quantitatively evaluated at each visit by the investigator on a scale of 0 (none) to 3 (severe). Tolerability of the treatment was evaluated at each visit from local skin reactions (LSRs) on a scale of 0 (not present) to 4 (high severity) for erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. Patients also rated pain at the treatment site within 15 minutes after each ALA application and blue light illumination using a 10 cm visual analog scale (VAS) that ranged from 0 (no pain) to 10 (worst pain possible).

Outcomes

The primary endpoint of the study was the proportion of patients achieving complete histological clearance of isSCC at the end of treatment (EOT). The secondary endpoints were the proportion of patients with CC of the treated lesion as measured by investigator assessment and the aesthetic appearance of the treated lesion as reflected by LSR scores.

No formal sample size calculation was performed for this study; the number of patients was determined based on the investigators' clinical judgment.

RESULTS

Patients

Thirty-two patients with a mean (range) age of 75 (54–95) years and Fitzpatrick skin types I, II, or III were enrolled. Two patients did not complete the study; one died of causes unrelated to the study treatment, and the other sought treatment outside the study. Among the 30 patients who completed the study, 20 (67%) were male, and 10 (33%) were female. The locations of the isSCC lesions were as follows: 7 (23.3%) on the left cheek or temple, 10 (33.3%) on the right cheek or temple, and 13 (43.3%) on the forehead (glabellar region or eyebrow). Overall, 15 (50%) lesions were located on the left side of the face and 15 (50%) on the right; none were located in the midface. The mean lesion diameter was 0.73 cm (range, 0.4–1.2 cm; standard deviation [SD], 0.20 cm). The mean lesion width was 0.59 cm (range, 0.4–1.1 cm; SD, 0.19 cm).

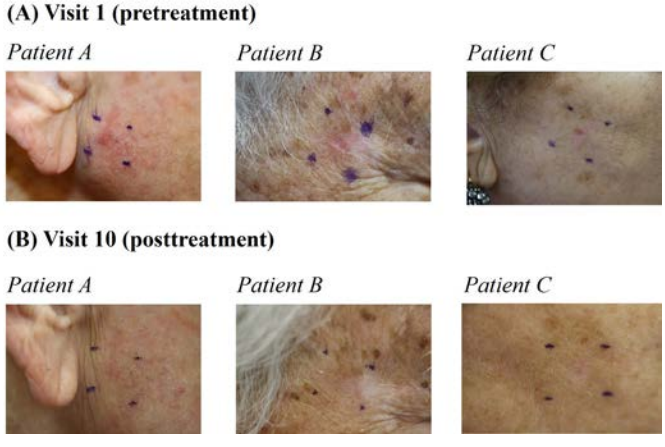
Effectiveness

All patients who completed the study (n = 30) achieved complete histological clearance of the treated isSCC lesion at EOT/surgical excision. All histological sections and surgical margins were free of neoplasm in every patient. Clinical clearance was also observed in all patients prior to surgical excision (Figure 1). One (3.3%) patient achieved CC by day 27, 12 (40%) by day 49, another 12 (40%) by day 58, and the remaining 5 (16.7%) by day 69. For context, the second blue light illumination occurred on day 29, and surgical excision was performed on day 58 (± 7 days after the second treatment).

Pigmentation Assessments

Almost all patients (29/30 [96.7%]) exhibited no changes in lesion pigmentation. One patient experienced mild hyperpigmentation 14 days after the first blue light treatment, which was resolved by the following visit 14 days later.

FIGURE 1. Imaging of facial isSCC before and after treatment with ALA-PDT.



ALA, aminolevulinic acid; isSCC, squamous cell carcinoma in situ; PDT, photodynamic therapy.

Local Skin Reactions

Erythema and flaking/scaling were the most common LSRs. Mean LSR scores for erythema and erosion/ulceration peaked on the day of each blue light treatment, one day after ALA application (visits 3 and 6; Table 1), whereas mean LSR scores for flaking/scaling peaked within 2 weeks after each blue light treatment. LSRs steadily decreased thereafter. Mean LSR scores were higher at visit 1 (pretreatment) than at visit 10 (EOT).

Tolerability

The mean pain score recorded by patients on the VAS within 15 minutes of each ALA application and each blue light treatment was 2.71 (range, 0–9; SD, 2.27).

TABLE 1.

Mean Local Skin Reaction Scores for the Lesion Areas						
Visit	Erythema	Flaking/Scaling	Crusting	Swelling	Vesiculation/Pustulation	Erosion/Ulceration
Visit 1 (pre-TX)	2.1	1.0	0.1	0	0	0
Visit 3 (TX1)	2.9	0.1	0	0	0	0.9
Visit 4 (FU1)	2.0	1.2	0.1	0	0	0
Visit 5 (pre-TX)	1.8	0.6	0	0	0	0
Visit 6 (TX2)	2.9	0.1	0.1	0	0	0.8
Visit 7 (FU2)	1.8	0.7	0.1	0	0	0
Visit 8 (FU3)	1.6	0.1	0	0	0	0
Visit 9 (FU4)	1.4	0.1	0	0	0	0
Visit 10 (EOT)	1.2	0	0	0	0	0

EOT, end of treatment; FU, follow-up; TX, treatment.

Safety

The treatment was well tolerated, with the majority of patients (28/30 [93.3%]) experiencing no adverse events (AEs). Reported AEs in 2 patients included newly diagnosed hypertension in one patient and worsening hypertension in another. Neither of these AEs was considered treatment related by the investigators, and they did not influence treatment administration or study outcomes.

DISCUSSION

ALA-PDT has emerged as a promising noninvasive treatment for superficial skin cancers. It has demonstrated efficacy for the treatment of isSCC as an alternative to current treatment modalities such as excisional surgery, 5-fluorouracil, and cryotherapy.[33,37,38] ALA-PDT is not approved by the US Food and Drug Administration for the treatment of isSCC.[35,39] Therefore, there is no standardized treatment protocol, and patient outcomes can vary due to the differences in photosensitizers, light sources and dosimetry, size and location of the lesions, and length of follow-up.[32,33,40,41]

Several studies show that ALA-PDT has clearance rates of 90% to 100% following 1 to 3 treatments in patients with isSCC.[38,42,43] In a retrospective study assessing the efficacy of ALA-PDT for the treatment of 58 patients with 68 isSCC lesions, 87.5% of lesions with a diameter of 2.0 cm or less cleared after 1 to 3 sessions of ALA-PDT using blue light. The initial complete response rate was 77.9%. The response rate was not associated with the number of PDT treatments, but it was linked to the location of the lesion on the face, tumor diameter of less than 2 cm, and longer ALA incubation time. Lesions with an incubation time of less than 3 hours had a response rate of 53.3%, while those with longer incubation had a response rate of 84.9%.[33] These studies highlight the correlation of a longer incubation period (>3 hours) with higher response rates, which was consistent with our study.

Another recent cohort study demonstrated that 85% of patients achieved histological clearance after 2 treatments using 20% ALA-PDT with pulsed dye laser for isSCC lesions on the face with a diameter of <2.0 cm. By the end of the treatment, only 2 patients experienced treatment failure, likely due to lesions in a cramped anatomical area (helix of ear and lateral malar cheek).[36] The study highlights the correlation of lesion characteristics, such as anatomical location and lesion size, with treatment success.

Although PDT has demonstrated similar efficacy to standard therapies, studies have shown that lesion size, incubation period, and anatomic location affect response rates.[33] Additionally, pretreatment abrasion, as recommended for the treatment of AKs, was not consistently documented in previous studies.[37,39,44] Our study used ALA-PDT with blue light to treat isSCC lesions located on the face after a 24-hour ALA incubation period. All patients achieved CC before eventual confirmation of complete histological clearance by the end of the treatment period. Our study thus supports existing literature, demonstrating the effectiveness of ALA-PDT treatment based on anatomic location, lesion diameter, and length of incubation and may highlight the importance of pretreatment abrasion.

Our findings also compare favorably with the reported efficacy of surgical excision and MMS, which are considered the gold standards for the treatment of isSCC and invasive SCC due to the high clearance and low recurrence rates achievable with these techniques.[45-47] In a retrospective study of 96 isSCC lesions, surgical excision with a 5-mm safety margin achieved a complete histological clearance rate of 94.4%, while smaller margins of <5 mm yielded clearance rates of 88.2% or lower. The overall recurrence rate after surgical excision was 2.1% over a mean follow-up of 35 months.[47]

In another study of 84 patients with isSCC lesions, standard excision achieved a 97.4% histological clearance rate over a follow-up of 12 months.[46] In contrast, MMS achieves better outcomes, with histologic clearance in all cases and a reported 5-year recurrence rate of 6.3%.[45] However, these surgical approaches may be associated with increased possibility of morbidity and less favorable cosmetic outcomes;[46,47] therefore, ALA-PDT may be preferable for patients with relatively small isSCC lesions in visible locations such as the face.

Our study demonstrated that complete clinical and histological clearance can be achieved using a nonsurgical, office-based protocol involving 24-hour ALA incubation and blue light illumination. Previous studies have also demonstrated the use of pulsed dye laser in addition to ALA-PDT with blue light, which was proved redundant by our protocol and data.[36] Our results are consistent with other published literature, specifically regarding clinical and histological clearance and safety profiles.[32,33,40,41] This may be attributable to our study design, which included pretreatment abrasion and a prolonged 24-hour ALA incubation. Treatment failure was not observed in our study, indicating a significant improvement in outcomes from previously published protocols that employed differing light sources, photosensitizers, and incubation times.[32-34,37]

The current 5-year cure rate for nonmelanoma skin cancer treated with MMS is >90%.[16,45,46] ALA-PDT would offer a safe, cosmetically appealing, more comfortable, and potentially less expensive alternative to MMS. Although all of our 30 patients had both clinical and histological clearance after 8 weeks, isSCC may recur 1 to 2 years after initial treatment.[32,33,37] Therefore, longer follow-up is needed to evaluate recurrence and other long-term outcomes after ALA-PDT in patients with facial isSCC.

CONCLUSION

Our study demonstrated that ALA-PDT is an effective, safe, and well-tolerated treatment strategy for facial isSCC. This approach achieved 100% clinical and complete histological clearance with minimal AEs and excellent cosmetic outcomes, reinforcing its potential as a noninvasive alternative to traditional surgical methods. While the results are promising, the study's limitations, including a small sample size and short follow-up period, highlight the need for further research. Future studies should explore the broader application of ALA-PDT, including efficacy on larger lesions, optimization of shorter incubation times, use on other anatomical sites, and long-term recurrence. In conclusion, ALA-PDT offers patients a safe and effective treatment option, particularly for lesions on cosmetically sensitive areas such as the face.

DISCLOSURES

MSN reports research grants from Biofrontera, Sirnaomics, and Sun Pharma, and is a consultant for Sirnaomics. AC, RJV, and VB have nothing to disclose.

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ORIGINAL ARTICLE

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Clinical Methodology to Evaluate the Efficacy of a Topical Cosmetic Eye Formulation on the Appearance of Dynamic Periorbital Lines

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ABSTRACT

Background: Dynamic lines in the periorbital region are the first signs of aging. Dynamic lines show only when emoting, possibly becoming static lines present with worsening with age.
Objective: This research was aimed at developing a novel methodology with the sensitivity to effectively evaluate the improvement of dynamic lines in the periorbital region by applying a topical cosmetic eye formulation.
Method: Female subjects aged 28–65 years with mild to moderate photoaging of all Fitzpatrick skin types were enrolled in a 12-week monadic study with evaluations at baseline and 2, 4, 8, and 12 weeks. A topical eye formulation was applied twice daily. Dermatologist evaluations of dynamic lines at maximum smile, static lines at neutral expression, and tactile evaluations of firmness and elasticity were obtained in addition to clinical photographs, subjective assessments, and instrumental noninvasive measurements of hydration and elasticity.
Results: After 12 weeks of twice-daily application, there was a statistically significant increase of 52% in cutaneous hydration, 183% improvement in viscoelasticity, 48% reduction in retraction time, and 58% in Young's modulus, demonstrating improved elasticity in the crow's feet area. 12-week investigator assessments revealed statistically significant improvements in the appearance of periorbital static lines (53%) and dynamic lines (33%). The tactile assessment methodology produced a 39% improvement in crow's feet pinch and 47% improvement in pinch recoil as measures of elasticity/hydration, and a 45% improvement in touch rebound as an assessment of firmness/hydration.
Conclusions: This research established the value of a novel dynamic line evaluation methodology to assess a topical cosmetic.

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INTRODUCTION

Dynamic lines in the context of aesthetic medicine can be defined as lines of facial expression and are typically treated with chemodenervation from injectable botulinum toxin.[1] These lines are created by muscle movement and are thus challenging to improve with topical products.[2] Consumer research shows that women are concerned with dynamic lines in the periorbital area, which may be one of the first visible signs of aging. At present, evaluation methods for topical treatments in this area are an unmet need.

The eye area is unique anatomically and socially. The periorbital skin is the thinnest on the entire body, making it the most susceptible to photoaging. However, the thinness is necessary to allow the eye to move, expressing emotion. The fine lines that appear under the eye and in the crow's feet area in the late twenties and early thirties are a sign of aging. These dynamic lines appear initially only with movement, but later are also present at rest as static lines with advancing age in the later thirties, early forties, and beyond. These dynamic and static periorbital lines worsen with time and are the most sensitive indicator of perceived age.[3] Minimizing and assessing the presence of these dynamic and static periorbital lines is an important unmet need in cosmetic science. This research was undertaken to establish the suitability of methodologies to evaluate periorbital lines in motion at maximum smile across a broad age range.

MATERIALS AND METHODS

Thirty-nine healthy female subjects with mild to moderate photoaging of all Fitzpatrick skin types, ages 28–65 years, were enrolled in this single-site monadic study to evaluate the effect of a targeted topical eye moisturizer on dynamic periorbital eye area lines at maximum smile when applied twice daily for 12 weeks. The population was stratified into two groups: younger female subjects ages 28–40 years, focusing on dynamic lines with minimal static lines (Group D), and older female subjects ages 41–65 years, focusing on dynamic and established static wrinkles (Group SD). Subjects who signed informed consent (Allendale Institutional Review Board (AIRB), Old Lyme, CT) and met all inclusion criteria and none of the exclusion criteria were enrolled at the baseline visit.

Subjects were asked to continue using their regular facial cleanser twice daily and stop using all other products on the face and eye area 3 days prior to study initiation. Following study enrollment, subjects were dispensed a cleanser (Liquid Facial Soap Mild for twice daily use and a Broad Spectrum SPF 50 sunscreen for morning application. They were provided with the blinded study eye formulation (from The Estee Lauder Companies Inc) for twice daily use in the periorbital area and a compliance diary. Subjects were allowed to continue applying color cosmetics for the prior 30 days as long as these cosmetics remained unchanged for the 12-week duration of the study. Subjects were evaluated for all assessments at baseline, week 2, week 4, week 8, and week 12.

The dermatologist, investigator, and subjects assessed the following eye area efficacy parameters visually: static periorbital lines at rest, eyes open, and dynamic periorbital lines at maximum smile, eyes open. All assessments were made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). The periorbital lines assessment was performed live at rest and in motion.

Elasticity was measured lateral to the right eye in terms of retraction time (R=milliseconds for the tissue to return to its original conformation after being distended by negative pressure vacuum pump), Young's modulus (E=megapascals required to lift the skin by the negative pressure vacuum pump), and viscoelastic properties (VE) combining the retraction time (R) and Young's modulus (E).

Noninvasive instrumental evaluations included the hydration pin probe (Cortex Technologies, Dermalab, Hadsund, Denmark) at the left lateral temple area to assess moisturization, as well as elasticity (Cortex Technologies, Dermalab, Hadsund, Denmark) measurements in the right temple area as a measure of skin viscoelastic properties.

Photographs were taken with eyes and mouth closed, with the face at rest and at maximum smile of the central, right, and left views with a Canfield VISIA CR4.3 (Canfield Scientific, Parsippany, NJ) camera system in standard lighting modes 1, 2, and 3 to document both static and dynamic periorbital facial lines (Figure 1).

The dermatologist investigator performed exploratory tactile evaluations in the eye area on a relaxed face with eyes open. The lateral crow's feet stretch test differentiates between etched crow's feet wrinkles versus crow's feet wrinkles that can be pulled out with skin stretching as a measure of elasticity. In the measure known as a lower eyelid pinch recoil test, the lower eyelid tissues were grasped between the thumb and forefinger and gently pinched to produce a tissue peak. The tissue peak was observed for the amount of tissue tenting and the duration

FIGURE 1. Representative static versus dynamic line image acquisition examples.

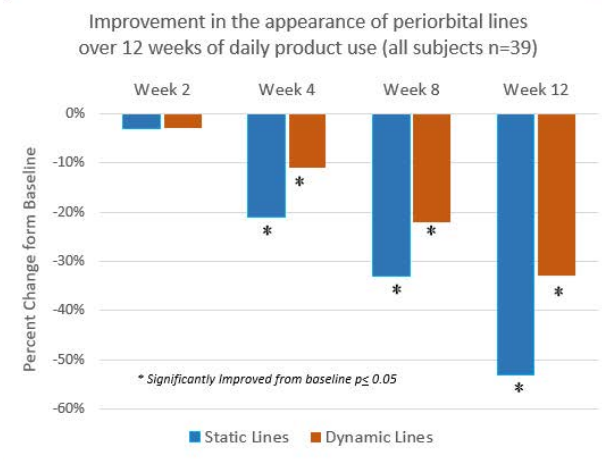
the tissue remained in place, evaluating the physical properties of the skin when stretched. This was an indirect assessment of lower eyelid elasticity and hydration. A lower eyelid touch rebound measure was performed, where the undereye tissue was indented with gentle pressure to observe the depth of lower eyelid indentation and how long the lower eyelid remained indented. Again, an indirect assessment of lower eyelid firmness and hydration, but based on compression of the lower eyelid tissues. The following rating scale was used for all three exploratory measurements: 0=very short recoil/rebound time, 1=short recoil/rebound time, 2=moderate recoil/rebound time, 3=long recoil/rebound time, 4=very long recoil/rebound time.

Investigator and subject ordinal nonparametric data were analyzed using the Wilcoxon signed rank test. Change was considered significant at a *P*-value of less than or equal to 0.05. The data were analyzed as one complete data set with subset analyses of dynamic periorbital lines performed for younger subjects with dynamic lines/minimal static lines (Group D) and older subjects with both dynamic lines/established static lines (Group SD).

RESULTS

39/39 subjects completed the study (n=20 in the younger Group D and n=19 in the older group SD) were enrolled across Fitzpatrick skin types I-VI, with the majority of subjects representing skin types I-II. No tolerability issues were identified by the subjects or investigator.

FIGURE 2. The dermatologist investigator assessed statistically significant improvement in static and dynamic lines at weeks 4, 8, and 12.



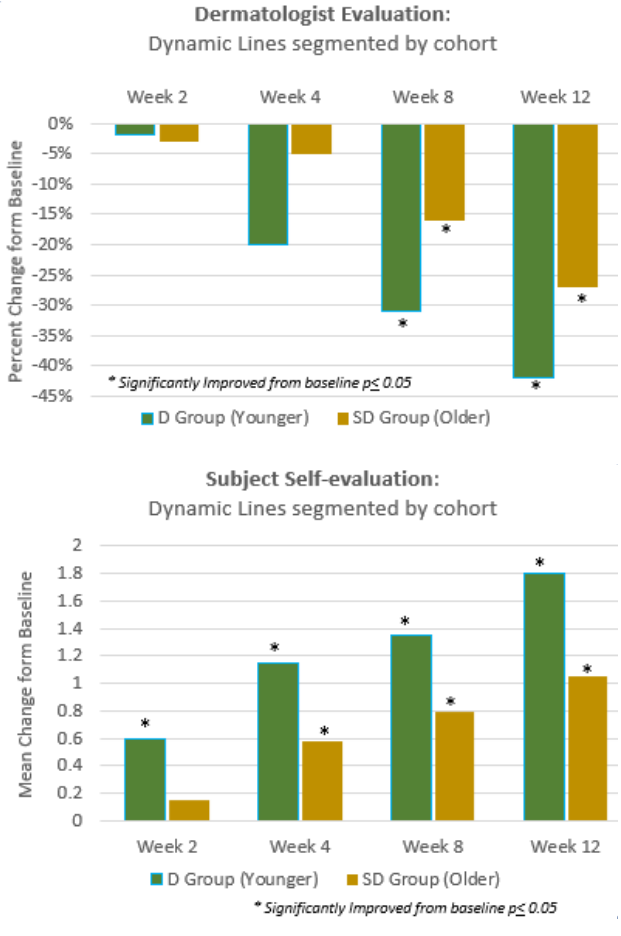
There was a gradual, consistent, statistically significant (P<0.001) increase in skin hydration. After 2 weeks of study formulation use, the skin water content increased 26%. This improvement continued into week 4 with a 42% increase and week 8 with a 37% increase. At the 12-week study completion, the skin water content had increased 52% over baseline in the lateral periorbital area.

There was a gradual improvement in all elasticity parameters with continued use of the study formulation. At week 12, there was a statistically significant improvement with a 48% reduction in retraction time, a 58% increase in Young's modulus, and a 183% improvement in viscoelasticity.

The investigator assessed the efficacy parameters of dynamic and static periorbital lines, which are presented in Figure 2. At week 12 study conclusion, both parameters were statistically significant (P<0.001) with continued improvement in static lines at rest (53%) and dynamic lines (33%) at maximum smile. The subjects were also asked to rate the same parameters with remarkably similar results to the investigator at week 12.

The data were analyzed separately for subjects with dynamic lines and minimal static lines (D) and those with both static and dynamic lines (SD) (Figure 3). Earlier, statistically significant improvement was rated by both the investigator and subjects with group D, probably due to less photodamage. However, by 12 weeks, statistically significant improvement (P<0.001) was seen in both groups. Notably, the percent improvement was greater among those with less photodamage in group D. Representative subject photographs are presented in Figure 4.

FIGURE 3. Subjects in the younger cohort demonstrated better periorbital dynamic line response to the study eye formulation as assessed by the dermatologist investigator.



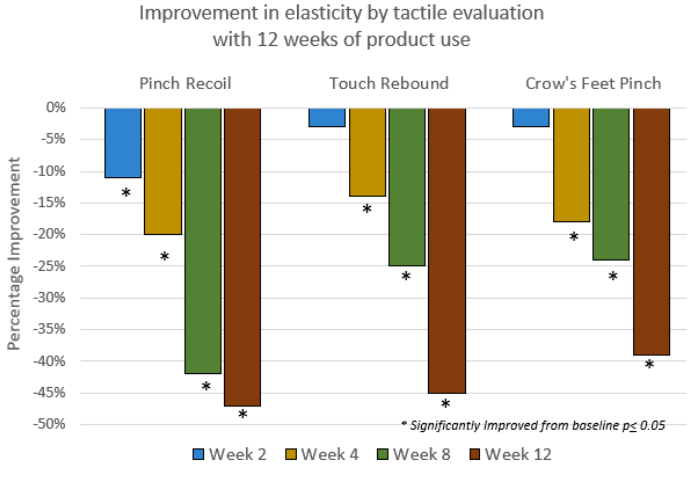
The dermatologist investigator utilized several methods of evaluating periorbital skin performance. Figure 5 summarizes the findings from the periorbital tests. The week 12 data demonstrated a 47% in pinch recoil, a 45% improvement in touch rebound, and a 39% improvement in crow's feet pinch. All values were highly statistically significant (P<0.001). These findings are consistent with the noninvasive, subject, and investigator assessments.

DISCUSSION

The first sign of facial aging across all Fitzpatrick skin types, all ethnicities, and all races is the presence of dynamic lines around the eyes. These lines appear with facial expression, especially smiling, and are necessary for interpersonal interaction to convey genuine interest. Thus, there is minimal distinction between attractive dynamic lines with facial expression and excessive

FIGURE 4. Representative younger and older subject periorbital dynamic line response to the study eye formulation.

FIGURE 5. Dermatologist investigator exploratory tactile eye assessments demonstrated a new method for capturing the effect of eye area moisturizers.



dynamic lines characteristic of aging.[4] While some choose to undergo botulinum toxin treatment to address dynamic lines, there is the challenge of leaving a natural facial expression with some dynamic lines, while alleviating the excessive dynamic lines, creating an aged appearance.

Many facial photoaging studies examine the presence of wrinkles and fine lines with a relaxed face.[6] This evaluates the appearance benefit of a formulation under optimal low wrinkle and fine line conditions, human facial expression is almost constant, making an assessment of the face in motion important. This research used a ghosting photo-overlay technique to capture consistent images of the face at rest and at maximum smile. The ghosting photo-overlay was essential to ensure that from visit to visit, subjects were emoting at the same maximum smile level. This allows assessment of dynamic wrinkles in real time and after study completion.

The research demonstrated an investigator-assessed, statistically significant 33% improvement in dynamic lines and a 53% improvement in static lines around the eye area at maximum smile after 12 weeks of study formulation use. Dynamic lines most prominently include lateral crow's feet lines as well as lower eyelid lines extending to include the entire inferior orbit. However, botulinum toxin is only approved to treat lateral crow's feet lines. Thus, at present, there is a need for topical cosmetics with firming and moisturizing properties to improve the lower eyelid area lines. Botulinum toxin and moisturizers obviously work differently, the former working by rapidly interrupting the neural transmission at the neuromuscular junction, and moisturizers affecting dynamic eye area lines by increasing skin water content over time. This improvement in skin hydration increases skin firmness and increases the force required to deform the skin. The increased deformation energy minimizes the puckering of the skin that is perceived as facial wrinkling and line formation. The study formulation increased skin hydration by 52% and increased skin viscoelasticity by 183% after 12 weeks of twice daily use. These mechanistic assessments verify the visually noted appearance improvement.

Exploratory physical assessments were also consistent with the positive visual and noninvasive assessments. Pinch recoil assessed skin firmness/thickness in the undereye area through pulling of the skin, which was improved by 47% at week 12. Touch rebound assessed skin firmness/thickness by pushing on the skin, which was improved through hydration by 45% at week 12. The crow's feet pinch assessed skin firmness/thickness through hydration lateral to the eye and was improved by 39% at week 12. These tactile tests of physical skin deformation and recovery supported the noninvasive and visual assessments.
This research examined improvement in dynamic eye lines utilizing several different assessment techniques to create an internally consistent data set. Topical eye products carefully formulated with moisturizing and firming properties can be used safely as a standalone product in younger individuals who are noticing dynamic lines as a first sign of facial aging, or they can be used as a supplemental topical product in more mature individuals who are undergoing chemodenervation treatments. New methodologies for evaluating dynamic lines in the lower and lateral eyelid areas may allow for better development of technologies for the improvement of aging in this important facial area.

CONCLUSION

This research presented and examined a comprehensive dynamic eye area line evaluation methodology for use in assessing topical formulations to address an early sign of photoaging.

DISCLOSURES

Martin Keh, Uma Santhanam, Kristine Schmalenberg, and Claude Saliou are employees of The Estee Lauder Companies Inc. Zoe Diana Draelos MD, is a researcher and consultant for The Estee Lauder Companies Inc. Elizabeth Bruning is a former Estee Lauder employee. Zoe Diana Draelos MD, received funding from The Estee Lauder Companies Inc. to conduct the research presented in this manuscript.

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ORIGINAL ARTICLE

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Advances in Gentle Polymeric Cleansing Technologies

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ABSTRACT

Modern skin cleansers have evolved from basic soaps to advanced cleansing formulations that also provide moisturization and skin barrier support. Surfactants work by emulsifying oils and reducing surface tension, but they may disrupt essential lipids in the skin, leading to barrier damage and sensitivity. Advances in surfactant technology have enabled the development of cleansers that combine efficacy with improved tolerability, foaming aesthetics, and reduced environmental impact. This review summarizes the evolution of modern mild skin cleansing technologies with a focus on polymeric cleansing technologies (PCTs) and the preclinical and clinical evidence of their efficacy and tolerability in sensitive skin. In vitro and in vivo studies have demonstrated that hydrophobically modified polymers (HMPs) and sodium hydrolyzed potato starch dodecenylsuccinate (SHPSD; NATRASURF™ PS-111) reduce irritation potential and surfactant penetration into the skin relative to commercial mild cleansers, while providing effective cleansing performance with favorable tolerability. In a 4-week clinical study involving participants with sensitive skin, a combination of the PCTs HMP and SHPSD demonstrated good tolerability and improved aesthetic skin parameters without compromising cleansing efficacy. Properly formulated cleansers incorporating PCTs can provide superior tolerance, improved skin and aesthetic outcomes, and effective cleansing. The complementary properties of HMP and SHPSD enable flexible formulation strategies that optimize cleansing results in healthy and sensitive skin.

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INTRODUCTION

The primary goal of a skin cleanser is to remove surface dirt, sweat, sebum, and contaminants without irritating or drying the skin. The key ingredients in cleansers include surfactants for cleansing, moisturizing agents (emollients) for counteracting dryness, preservatives, and fragrances.[1] Surfactants solubilize hydrophobic material into the aqueous phase, enabling its removal from the skin surface. Cleansers help maintain hygiene but may damage the skin barrier, worsening sensitive skin conditions,[2] because surfactants cannot distinguish between unwanted lipophilic debris and the essential intercellular lipids protecting the skin.

A wide range of skin cleansers exists, generally falling into two types: soap-based and synthetic detergents (syndets).[2] Soap was the first documented cleansing agent, used since the eighth century, with the saponification process published in 1775.[3] Soaps are anionic surfactants and often irritating due to their alkaline nature and tendency to form insoluble salts in hard or sea water. Over time, consumer expectations expanded to include health, cosmetic, and environmental benefits.[3,4]

The development of soap-free syndets in the 1940s was a major breakthrough, enabling milder cleansing.[5] Like soaps, syndets are amphiphilic molecules that function as wetting and foaming agents, and emulsifiers.[5] Made without a strong base, they do not alter skin pH as soaps do. Syndets vary and may be anionic, cationic, amphoteric, or non-ionic detergents, each with different effects on irritancy and toxicity.[5] Like soaps, syndets are soluble in water and organic solvents, and their detergent properties can disrupt the skin barrier (Table 1).[5,6] Lipid-free cleansers are neutral pH liquids that clean without fats and can be removed without water. They contain fatty alcohols and humectants that leave a moisturizing film and are recommended for dry, sensitive, or compromised skin.[7]

This evolution of cleansers provides skin care benefits beyond cleansing and forms a range of cosmetic products that vary in mildness, moisturizing efficacy, aesthetics (feel, creaminess, fragrance, foaming/lather), and other factors. Effective cleansers based on mild syndets and/or emollients that minimally interact with the stratum corneum structure help minimize the potential damage to skin and are helpful for patients with a compromised

TABLE 1.

Differences Between Soaps and Synthetic Detergents	
Soaps	**Synthetic Detergents**
Sodium or potassium salts of a long chain of carboxylic acids	Sodium alkyl sulfates or sodium alkyl benzene sulfonates
Made from natural compounds (eg, vegetable oils, animal fats)	Made from petrochemicals derived from petroleum, or produced using oleochemicals derived from renewable plant oils and animal fats
Relatively weak cleansing action in hard, acidic, and saline water	Effective cleansing action in hard, acidic, and saline water
Form scum with hard water	Form lather with hard water
Mostly biodegradable	Non-biodegradable
Anionic	May be cationic, anionic, amphoteric, or non-ionic
Examples: sodium stearate/potassium cocoate	Examples: sodium lauryl sulfate, sodium cocoyl isethionate

skin barrier.[8] Non-foaming mild cleansers may not be as well accepted as cleansers with foaming action, which enhances the "perception of effectiveness/feeling of clean" experience, even though foaming itself is not required for effective cleansing.[9] Skin cleansers formulated with less or no surfactant may be ineffective at removing sebum and impurities and can leave a residue after rinsing. Syndet-based surfactants derived from non-renewable sources (eg, petroleum) contribute to environmental concerns, whereas surfactants sourced from renewable ingredients permit greener chemistry within personal care.[5]

Polymeric cleansing technologies (PCTs) represent a novel approach that balances effective skin cleansing with preservation of the skin barrier by incorporating polymers that enhance cleansing efficacy and sensory attributes while minimizing the risk of skin damage. Hydrophobically modified polymers (HMPs) interact with free surfactant molecules to form polymer-surfactant complexes, which reduce surfactant penetration into the skin and limit surfactant activity at the skin surface, thereby decreasing irritation potential.[10] These polymers also contribute to improved lathering and foaming,[11] rinsability, and skin hydration, providing particular benefit for patients with sensitive skin conditions (eg, atopic dermatitis [AD], rosacea, and eczema).[12] The polymeric surfactant (PS) sodium hydrolyzed potato starch dodecenylsuccinate (SHPSD; NATRASURF™ PS-111) is a low molecular weight hydrolyzed potato starch homogeneously substituted with hydrophobic dodecenylsuccinate ester groups, with high surface activity and mildness.[13]

This narrative review discusses the versatility of PCTs in delivering effective and well-tolerated cleansing across different skin types. Additionally, it summarizes the development, tolerability, and clinical efficacy of two proprietary PCTs, HMP and SHPSD (Johnson & Johnson Consumer Inc., a subsidiary of Kenvue Inc., Skillman, NJ), and their versatility and benefits, including for sensitive skin conditions. This review also evaluates the contribution of combining PCTs with other active ingredients to the overall performance of a cleansing formulation. Relevant preclinical and clinical studies evaluating the role of PCTs in dermatologic disorders were identified based on the experience and knowledge of the authors. A literature review (systematic or non-systematic) was not conducted.

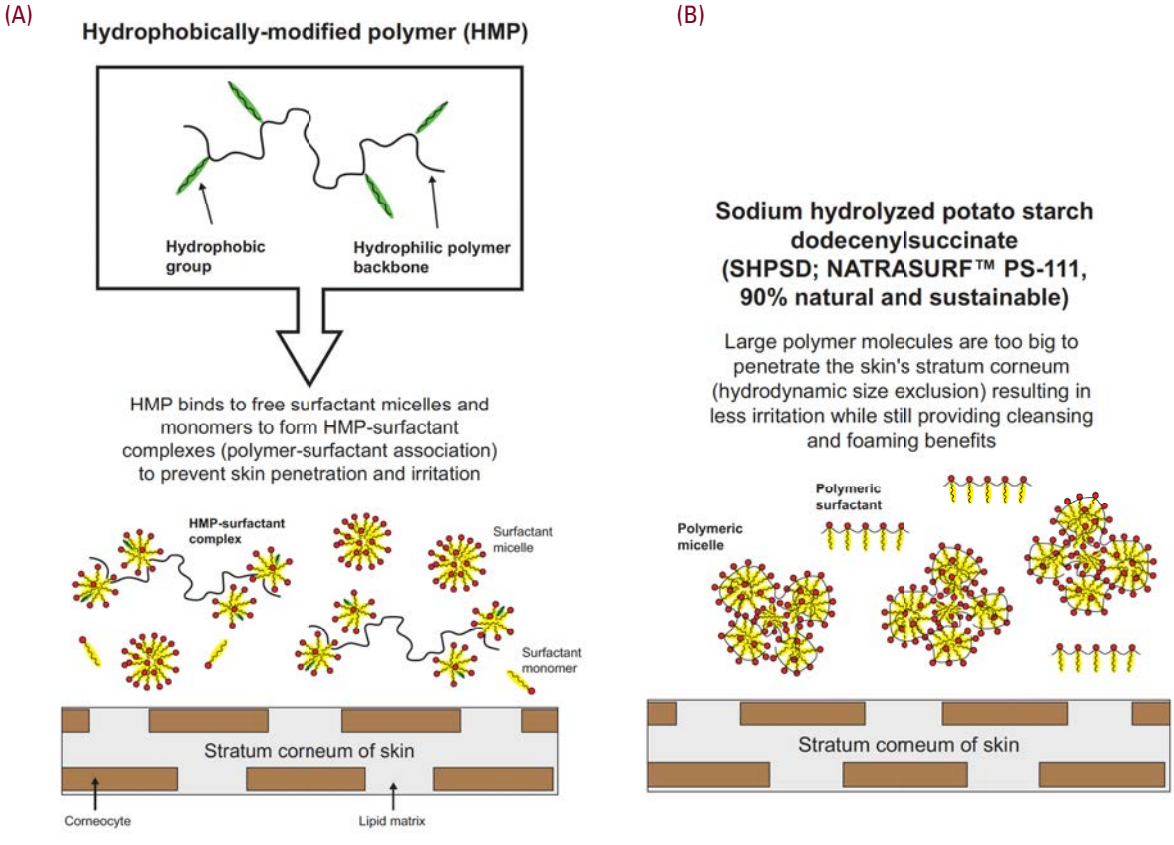
Value and Adaptability of PCTs

Gentle skin cleansing is particularly important for patients with a compromised skin barrier, such as those with sensitive skin, cosmetic intolerance, acne, psoriasis, rosacea, and AD, or individuals who have undergone cosmetic surgery procedures.[14] Compared with individuals with normal skin, these patients are more susceptible to dryness, irritant contact reactions, and allergic responses, making the selection of a compatible cleanser especially important. Mild cleansers are generally recommended as they provide effective cleansing without disrupting the skin barrier,[14] and can be used alongside topical therapies.[15]

Skin barrier function naturally deteriorates with age, and xerosis and pruritus (itch) are common.[16,17] The recovery of skin barrier function against irritation from surfactant or alkaline soap is slow in the elderly; therefore, a lipid-free cleanser with a mild surfactant and emollient is helpful.[15] Beneficial supplementary ingredients in cleansers could include urea or menthol with anti-itch properties.[18] Dry skin in people with pigmented skin can have a whitish coloring, known as "ashiness." This condition can also benefit from a mild and moisturizing cleanser.[19]

The tolerability of a cleanser depends on several factors, including: pH, type and concentration of surfactants, inclusion of moisturizing agents, and amount of residual residue after washing.[14,20] Each of these elements can influence skin irritation, hydration, and overall comfort. Mild cleansers should interact minimally with skin proteins and lipids, have a similar pH to the skin, and contain moisturizing agents.

FIGURE 1. Modes of Action of (A) HMP and (B) SHPSD (NATRASURF™ PS-111)[11]



HMP, hydrophobically-modified polymer; SHPSD, sodium hydrolyzed potato starch dodecenylsuccinate.
Reprinted ("Adapted" or "in part") with permission from Fevola MJ, Walters RM, LiBrizzi JJ. A New Approach to Formulating Mild Cleansers: Hydrophobically-Modified Polymers for Irritation Mitigation. In: Morgan SE, Lochhead RY, eds. Polymeric Delivery of Therapeutics. American Chemical Society; 2010:221-242:chap 12. ACS Symposium Series; vol 1053. Copyright © 2010, American Chemical Society.

Traditional surfactants have a more pronounced damaging effect on compromised skin.[5] AD can be worsened by intracellular lipid loss, resulting in a red, scaly appearance.[21] Facial rosacea is also associated with an impaired or overly permeable skin barrier, which allows irritants to penetrate the skin and trigger inflammation and vasodilation, characterized by increased trans-epidermal water loss.[22] The use of traditional surfactants reduces tolerance to common skincare products, worsening rosacea symptoms, and stinging and burning sensations, all factors associated with compromised skin barrier integrity.[23]

An HMP-containing facial cleanser that delivers cream-to-foam properties was evaluated for mildness, self-perceived skin benefits, tolerance, impact on pH, and diversity of the microbiome in a 4-week clinical study in 36 female patients with sensitive, reactive skin.[24] Testing on human epidermal skin equivalents showed that the HMP cleanser was mild and preserved the skin barrier, as evidenced by significantly lower interleukin-1α (IL-1α) levels and significantly higher trans-epithelial electric resistance (TEER) values compared with a harsh cleanser (P<0.05 for both). This HMP-containing cleanser demonstrated a good tolerability profile, with no significant increase in erythema, burning or stinging, or dryness, while maintaining skin pH and the natural microbiome in women with sensitive, reactive skin.[24]

PCTs can be combined with other active ingredients to address specific skin conditions and enhance overall efficacy. A study compared a conventional salicylic acid-surfactant cleanser with a PCT cleanser containing salicylic acid (SA) in a microgel complex and SHPSD (SA-PCT cleanser).[25] SA has exfoliating, sebum-reducing, and anti-inflammatory benefits, which are helpful for acne-prone skin. The inclusion of SA in a microgel complex enhances its penetration and delivery, thereby improving the overall acne efficacy of SA.[26] In the preclinical phase of this study, the skin barrier effects of the two cleansers were evaluated in human epidermal equivalents. The SA-PCT cleanser maintained skin barrier integrity and function without causing

hyperkeratinization, as demonstrated by significantly higher TEER and reduced IL-1 α release compared with the conventional cleanser.[26] These preclinical data demonstrate the efficacy and tolerability of PCTs compared with traditional surfactant systems in sensitive or compromised skin types.

Hydrophobically modified polymers (HMPs)

Surfactants have an amphiphilic structure, consisting of both a hydrophilic polar head group and a nonpolar lipophilic tail, which drives the surfactants to oil/water interfaces, forming droplets known as micelles, to facilitate cleansing. However, during the cleansing process, surfactants can adsorb onto and diffuse into the skin, disrupting the stratum corneum lipid structural order and causing degradation of the skin barrier. Consequently, inflammation and oxidative stress can occur, causing redness, dryness, discomfort, or irritation of the skin.[14,27] Anionic surfactants (eg, sodium lauryl sulfate in syndets) are the most common surfactants used in personal care products.[5] They have good cleansing and lather properties, but can irritate the skin and eyes.

HMPs were developed as an advanced technology to reduce cleanser-associated damage and are designed to remain on the skin's surface without penetrating the skin.[27] Low molecular weight HMPs, eg, potassium acrylate copolymer, can form larger polymer-surfactant complexes that are less irritating to the stratum corneum lipid barrier when combined with surfactants.[9,20,28] HMPs and HMP-surfactant complexes are capable of increasing the quality of foam bubbles (thickness and viscosity), resulting in thicker, longer-lasting foam.[11]

The effect of a foaming formulation containing HMP versus a lotion facial cleanser on the skin barrier was demonstrated using multiphoton laser scanning in a skin permeability study.[29] Less fluorescence (lower dye penetration) was observed in the HMP-treated compared with the lotion cleanser–treated skin specimens, corresponding to reduced barrier damage with the HMP cleanser.[29]

Surfactant-based cleansing formulations containing HMPs are composed of a lower concentration of free surfactant micelles and polymer-surfactant complexes.[30] In vitro studies and patch testing in human participants demonstrated that such HMP-containing cleansers are less aggressive to the skin than other commercial mild cleansers, preventing irritation while ensuring effective cleansing.[25,30] A randomized, double-blind, 3-week study compared a foaming cleanser containing an HMP (potassium acrylates copolymer), glycerin, and a surfactant system with a commercial nonfoaming cleanser without HMP in women with mild-to-moderate eczema, rosacea, AD, or active acne. Both cleansers were equally effective and well accepted, with greater improvements in evaluated skin categories and less irritation noted with the HMP-containing test cleanser.[12] Endpoints included facial irritation attributes (eg, stinging, erythema, burning) or the worsening of eczema, AD, acne, or rosacea after 3 weeks of use. Secondary endpoints included the investigator's assessment of facial dirt, cosmetics, and sebum removal. The HMP formulation, versus the commercial nonfoaming cleanser, provided superior tolerability, rinsability, and makeup removal. The HMP cleanser also provided significant improvement in skin condition according to patients' self-assessment.[12]

A pooled analysis of 14 clinical studies including 800 individuals showed that an HMP cleanser was well tolerated alone or in combination with various treatments, including light therapy, alpha or beta hydroxy acids, polyhydroxy acids, benzoyl peroxide, retinol, and hexyl resorcinol.[31] In three clinical studies evaluating the efficacy of an HMP cleanser as the primary test product in individuals with various skin types, including acne-prone and sensitive skin, the HMP cleanser demonstrated equivalent or superior efficacy in makeup removal compared with a leading gentle cleanser, was well tolerated, and had no detectable effect on the skin microbiome after 4 weeks.[31]

Sodium hydrolyzed potato starch dodecenylsuccinate (SHPSD)

Consumers increasingly expect skin cleansers to offer more than effective and non-irritating cleansing, demanding a holistic, enjoyable, and sensory experience through specific textures, scents, and aesthetics, eg, foaming consistency. The selection of ingredients is therefore crucial to ensure the optimal characteristics in a cleanser and improve acceptability and satisfaction. The lather or foaming effect produced when a surfactant interacts with water provides a luxurious sensory experience and helps to spread the product, making it easier to cover more of the body area with less product, ensuring a milder and more even cleanse. In general, it has been demonstrated that the less time a cleansing agent remains on the skin, the less irritation potential it may have.[15,32]

It was initially believed that only surfactant monomers could penetrate the stratum corneum and not surfactant micelles due to their larger size,[20] based on observations that the critical monomer concentration (CMC: the upper limit of monomer concentration in a solution) was positively correlated with surfactant-induced irritation.[33] More recently, it was demonstrated that skin irritation and barrier disruption increase with increasing concentration of surfactant, even at surfactant concentrations above the CMC.[20] At the typical concentrations of surfactant used in cleansers, nearly all the surfactants exist in micelles, with only a very small fraction as monomers, and they can interact with the skin and contribute to irritation.[20] This suggests a more complex mechanism of surfactant interaction with the skin.

As both monomers and micelles present in surfactants can penetrate into the stratum corneum of the skin during cleansing,

the addition of HMPs to surfactant-based cleansers can help mitigate interaction with the skin by forming complexes that reduce surfactant penetration into the skin and maintain skin barrier integrity.[27,30]

The starch-based SHPSD (NATRASURF™ PS-111) can provide the cleansing and foaming of a traditional surfactant with virtually no irritation potential due to a hydrodynamic size exclusion mechanism, whereby the PS and PS micelles are too large to penetrate the skin layers and cause irritation.[13] SHPSD is a proprietary biodegradable polymer developed using green chemistry principles involving the modification of naturally occurring polysaccharides, which are renewable, resulting in minimal environmental impact throughout its life cycle.[13] This makes it a sustainable alternative to traditional surfactants in personal care products. PSs can be combined with conventional surfactants to form larger mixed micelles with improved mildness versus traditional surfactant blends, while still providing a foaming action.[13]

In a 12-week facial study including 35 participants, an acne cleanser containing SA-SHPSD in a microgel complex (which improves the penetration and delivery of SA), demonstrated significant reductions in the number of non-inflammatory and inflammatory lesions from week 4 to week 12 (end of study).[25] Self-assessments further indicated consistent improvements in acne-related parameters.[25] In addition, in a 5-day arm wash study, the SA-PCT cleanser demonstrated lower water loss and clinical scores for dryness and erythema. These clinical results support the efficacy of the SA-SHPSD formulation in maintaining the skin barrier while providing improvement of acne-prone skin.[25]

HMP and SHPSD combination

HMPs bind surfactants independently of hydrodynamic size, meaning unbound micelles may vary in size, including smaller unbound micelles capable of penetration into the skin.[34] HMPs must therefore be correctly matched to the surfactant(s) in the cleansing system to ensure high surfactant binding efficiency.[34] HMP combined with PS, such as SHPSD (PS-111), can produce a cleansing system with an overall greater micelle size, further minimizing surfactant penetration into the skin while also providing foaming capabilities at the skin's surface.

In a 4-week clinical study, the suitability of a facial foaming gel cleanser with PCT was assessed in a diverse population of 85 people with sensitive skin conditions (eczema/AD, rosacea, acne, or cosmetic intolerance syndrome).[9] The cohort included approximately one third of participants who were Black/African American or Asian, and a range of Fitzpatrick skin types (75% Types I–III, 25% Types IV–VI). The cleanser consisted of two PCTs: potassium acrylate copolymer (HMP) and SHPSD combined with mild surfactants. Potassium acrylate copolymer associates with other surfactants in the formulation to create HMP-surfactant complexes,[34] while SHPSD forms mixed micelles with the surfactants and surfactant complexes, preventing skin penetration via hydrodynamic size exclusion.[34] Tolerability and efficacy were evaluated via investigator grading, self-assessment questionnaire, noninvasive measurements, and digital photography. The foaming gel cleanser was well tolerated, showing no significant increases in investigator-graded irritation endpoints, with a significant reduction in markers of skin sensitivity at 2 and 4 weeks. Improvements in smoothness, softness, clarity, radiance, and overall skin appearance were also observed by the investigator and patients at 2 and 4 weeks.[9] This study provides clinical evidence that a properly formulated cleanser with foaming properties is tolerated in clinically diagnosed sensitive skin and provides additional benefits such as improved skin appearance. This foaming attribute of a cleanser is a preferred consumer aesthetic that may promote compliance in persons with clinically diagnosed sensitive skin as long as it is non-irritating.[9] The HMP SHPSD formulation also contained the humectants glycerin and hyaluronic acid, ingredients that further support skin hydration and minimize irritation. PCT can therefore offer tolerability benefits beyond basic cleansers and is a versatile class of ingredients that can be applied across various cleansing products, including hair and body washes.

DISCUSSION

Recent advancements in cleanser technology focus on milder surfactants, neutral or acidic pH levels, and the inclusion of beneficial active ingredients to support the skin barrier and reduce irritation. PCT enables less aggressive cleansing solutions that can be adapted in various product formats suitable for different skin and body needs and types.

Innovations like HMP and SHPSD minimize stratum corneum disruption and, therefore, irritation potential while providing effective cleansing performance.[12,13] HMP manages the concentration of free surfactants that are potential skin irritants via a polymer-surfactant association mechanism. The SHPSD polymer is a PS based on a hydrodynamic size exclusion, which contributes to its mildness and effectiveness. Both PCTs have demonstrated less irritation potential and decreased surfactant penetration into the skin compared with traditional surfactants in in vitro tests and in vivo clinical studies.[10] The combination of an HMP and a PS demonstrated good tolerability and improvements in aesthetic skin parameters in a 4-week clinical study in people with sensitive skin conditions.[9] These PCTs can also be effectively used alongside other active skincare ingredients, whether combined in the same formula or used separately.[25,31]

CONCLUSION

Over the years, skin cleansers have progressed from basic high pH soaps to milder syndets and lipid-free cleansers.

Newer technologies now exist to meet consumer expectations for cleansers that are mild, provide skincare benefits, and can be easily rinsed. The addition of PS to cleansing systems can provide superior cleansing performance with minimal disruption of the skin barrier, a known issue with traditional surfactant systems. Properly formulated cleansers also provide additional benefits over effective cleansing, such as superior tolerance, improved skin appearance, and desirable aesthetic properties. The properties of HMP and SHPSD permit their use alone or together to create a cleansing product that achieves optimal results in the management of various dermatologic disorders.

DISCLOSURES

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CASE REPORT

Journal of Drugs in Dermatology

Pembrolizumab as an Off-Label Treatment of Facial Angiosarcoma: A Case Report

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ABSTRACT

Summary of Case: We report an atypical case of cutaneous angiosarcoma presenting as unilateral nasal swelling in an elderly male. The lesion was unresponsive to topical and antibiotic therapy. Diagnosis was confirmed after surgical excision, and disease control was ultimately achieved through radiation and off-label use of pembrolizumab.

Patient Info: A 79-year-old male with a history of squamous cell carcinoma presented with a 1–2 month history of erythematous, scaly swelling of the left nasal tip and ala. Family history was notable for nonmelanoma skin cancer.

Diagnosis: Initial differential diagnoses included contact dermatitis, rosacea, and rhinophyma. A shave biopsy revealed actinic damage but no malignancy. Following persistent symptoms and referral to plastic surgery, debulking surgery was performed. Histopathology confirmed cutaneous angiosarcoma.

Treatment: The patient declined wide local excision and instead underwent a 4-week course of hypofractionated radiation. Subsequent imaging showed regional lymph node recurrence. He declined biopsy and surgery, and was started on off-label pembrolizumab immunotherapy for disease control.

Outcome: Following immunotherapy, the patient experienced sustained remission with no clinical or radiographic evidence of disease four years post-treatment.

Discussion: Cutaneous angiosarcoma is a rare, aggressive malignancy with a poor prognosis. This case illustrates the importance of considering angiosarcoma in atypical facial lesions and demonstrates disease control using a non-traditional, patient-centered treatment strategy. Immunotherapy with pembrolizumab may offer a promising option in select patients, particularly those with contraindications to extensive surgery.

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INTRODUCTION

Cutaneous angiosarcoma is a rare, aggressive malignant neoplasm of vascular endothelial cell origin with a poor prognosis, due to its rapid growth and propensity for local recurrence and distant metastasis.[1,2] The typical presentation of cutaneous angiosarcoma involves a progressive, bruise-like lesion on the head or neck.[2] In most cases, the scalp is the predominant site affected, while other less commonly affected areas include the trunk and extremities. Cutaneous angiosarcoma, despite its poor prognosis, is extremely rare accounting for less than 1% of all sarcomas.[3] The incidence rate is approximately 3.3 cases per 1,000,000 person-years, with higher prevalence in those over 70 years of age.[3] As Wagner et al (2024) highlight, the increase in cases within a 20-year period emphasizes the need for early detection and treatment. Current treatment for cutaneous angiosarcoma includes a multimodal approach due to its aggressive nature and high recurrence rate. Treatment plans usually include wide local excision, radiation therapy, and chemotherapy.[4]

We present an atypical case of facial angiosarcoma arising as an asymmetric, non-purpuric swelling of the left nasal tip and ala, treated unconventionally with debulking surgery, radiation therapy, and off-label pembrolizumab immunotherapy. These treatment paradigms aligned with the patient's goals as they navigated concerns of wide local excision due to cosmesis and quality of life. The patient is doing well four years later and will resume surgery or radiation if needed for any recurrence.

Case Presentation

A 79-year-old male with a history of squamous cell carcinoma presented to the dermatology department with a chief concern of "swelling" on the left side of the nose for the past 1–2 months. He reported his symptoms on the left side of the nose as "red", "swollen", "somewhat scaly", and "not itchy". The patient has a family history of nonmelanoma skin cancer. The dermatologic exam revealed an erythematous, ill-circumscribed nodule at the left nasal tip, eliminating the left alar groove, positive for

FIGURE 1. Initial presentation. Smooth, pink nodularity to the left nasal tip and ala.

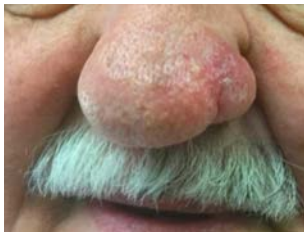
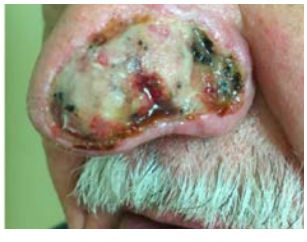


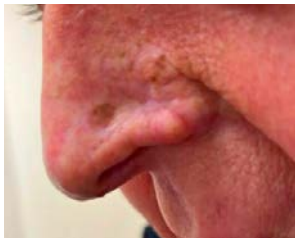
FIGURE 2. After tangential excision of the tumor. Angiosarcoma is widely positive at the base of the lesion.



overlying scales. (Figure 1) The differential included dermatitis, rosacea, or unilateral rhinophyma. The initial treatment was fluocinonide 0.05 % topical ointment two times a day for two weeks. After the treatment course was complete, the patient returned two weeks later, and the dermatologic exam revealed bulbous erythematous swelling of the left side of the nose with a small central ulcer. The differential diagnosis was expanded to include basal cell carcinoma and rhinophyma. A shave biopsy of the lesion was obtained and revealed actinic damage but no skin malignancy. There were no improvements with the initial treatment of fluocinonide, so the patient was prescribed doxycycline 100 mg two times a day, mupirocin 2% ointment applied twice daily for 2 weeks, and referred to the Head and Neck Surgery (HNS) department for further evaluation and management.

The HNS department agreed with the possible differential of actinic keratosis or rhinophyma, with recommended monitoring. In the next follow-up appointment, the plan was to refer the patient to the Plastic Surgery department for surgical excision. The excision from the Plastic Surgery department was sent to pathology, and the result revealed angiosarcoma transected at the base. The recommendations included surgery and radiation, but the patient declined the surgery and chose to move forward with a hypofractionated 4-week course of radiation therapy. The patient underwent the full course of radiation therapy with expected side effects of fatigue, dermatitis, and nasal cavity mucositis. A follow-up PET scan showed decreased hypermetabolic activity in the nose and nasal cavity compared to the prior exam. After treatment completion, a PET scan was performed four months later, and

FIGURE 3. Angiosarcoma after surgical excision with positive margins, radiation therapy, and pembrolizumab immunotherapy.



the results revealed the suspicion of regional recurrence of the nasal angiosarcoma in the left submandibular lymph nodes and left parotid lymph node, which prompted a CT-guided biopsy for confirmation. The patient refused biopsy and surgery, which led the team to consider palliative radiation therapy. The care team concluded that the use of pembrolizumab for palliation of the recurrent angiosarcomas would be a systemic approach to addressing the recurrent angiosarcoma. The course treatment of pembrolizumab led to no current evidence of angiosarcoma.

DISCUSSION

Angiosarcoma of the head and neck is a rare vascular sarcoma associated with high rates of local recurrence, distant metastasis, and a poor prognosis. However, several studies comparing face and scalp angiosarcomas have shown improved prognosis when angiosarcoma occurs on the face.[5] A meta-analysis by Shin et al showed improved prognosis in patients less than 70 years old, tumor size less than 5 cm, treatment with surgical resection (vs radiation or chemotherapy alone), negative surgical margins after resection, and tumor location on the face as opposed to the scalp.[5] Our case mostly supports this trend since the tumor location was on the face, the tumor size was less than 5 cm, and surgical resection was performed.

Angiosarcoma is typically treated with multiple modalities, including surgery, radiotherapy, and chemotherapy. Our patient's angiosarcoma was controlled with debulking surgery, radiation therapy, and pembrolizumab. Pembrolizumab is a humanized antibody that targets the programmed cell death protein 1 (PD-1). PD-1 functions as an immune checkpoint receptor that inhibits the activation of T-cells, inevitably allowing cancer cells to evade immune surveillance.[6,7] (Blay 2023, Ravi 2017) pembrolizumab is used in cancer immunotherapy and is currently FDA approved for a variety of malignancies, including melanoma, non-small cell lung cancer, squamous cell carcinoma, and Merkel cell carcinoma. Although currently being used off-label in angiosarcoma, there are multiple case reports in the literature showing a sustained response of angiosarcoma to PD-1-directed therapy.[7]

It is theorized that PD-1 inhibitors, like pembrolizumab, show efficacy in treating cutaneous angiosarcoma by restoring

the immune system's ability to recognize and destroy cancer cells.[6,7] In conjunction with multimodal treatment, checkpoint inhibitors may serve a beneficial role in controlling disease, especially in cutaneous angiosarcoma, where there is a high recurrence rate and poor prognosis. The following factors must also be considered, such as tumor location, size, age of the patient, and surgical intervention, which have been shown to influence outcomes positively. Our case aligns with existing literature that indicates improved prognosis for angiosarcomas located on the face. Additionally, the use of immunotherapy, specifically pembrolizumab, has shown promise in controlling angiosarcoma, suggesting potential for further research and clinical application in this aggressive malignancy.

DISCLOSURES

The authors have no conflicts of interest to declare or financial disclosures.

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CASE REPORT

Journal of Drugs in Dermatology

Treatment of Confluent and Reticulated Papillomatosis Using Fixed-Dose Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel

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ABSTRACT

Introduction: Confluent and reticulated papillomatosis (CARP) is a rare, non-systemic disease usually treated using oral antibiotics.
Case Presentation: We present a 15-year-old male with CARP for whom initial treatment with doxycycline, ketoconazole shampoo, and topical minocycline was ineffective. He was subsequently treated with a combination of fixed-dose triple-combination clindamycin phosphate 1.2% / adapalene 0.15% / benzoyl peroxide 3.1% (CAB) gel and a sodium hypochlorite-based body wash, resulting in complete clearance after 3 months.
Discussion: CARP is most often treated with oral or topical antibiotics. This case highlights the successful use of topical combination therapy with CAB, which is FDA approved for acne, plus a sodium hypochlorite-based body wash as a safe and effective alternative.
Conclusion: This case supports the potential role of CAB in CARP management and highlights the value of non-systemic options for treatment-resistant cases.

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INTRODUCTION

Confluent and reticulated papillomatosis (CARP) is a chronic dermatologic condition characterized by multiple hyperpigmented papules that converge to form plaques or patches and reticulate peripherally. The etiology of CARP remains unclear, but current evidence most strongly supports bacterial association and abnormal keratinization.[1] Oral antibiotics are the most frequently used first-line therapy for treating CARP.[2] The authors present a case of CARP treated successfully with topical fixed-dose triple-combination clindamycin phosphate 1.2% / adapalene 0.15% / benzoyl peroxide 3.1% (CAB) gel as a novel treatment.

Case Presentation

A 15-year-old Caucasian male presented with an itchy, discolored rash on his epigastric region for the past several months. Physical examination revealed confluent and reticulated brown patches on the epigastric lesions (Figure 1). A punch biopsy was performed with a clinical differential diagnosis that included tinea versicolor and CARP. Histopathology revealed hyperkeratosis, papillomatosis, and mild acanthosis, confirming the diagnosis of CARP. The patient demonstrated refractory

FIGURE 1. Initial presentation showing hyperpigmented, reticulated patches in the epigastric region consistent with CARP.

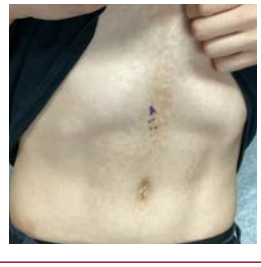


FIGURE 2. Persistent CARP lesions after a daily trial of ketoconazole 2% shampoo, minocycline foam 4%, and doxycycline 100 mg for 3 months.

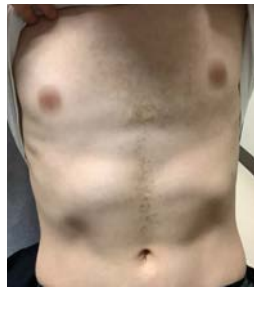
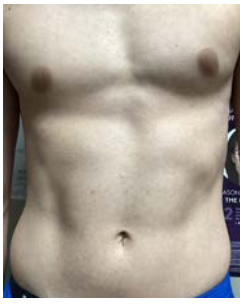


FIGURE 3. Three months after beginning daily CAB and sodium hypochlorite-based body wash the lesions, itch and pigmentation had cleared.



disease despite a 3-month course of daily ketoconazole 2% shampoo, topical minocycline 4% foam, and oral doxycycline 100 mg (Figure 2). He was subsequently started on daily CAB and CLn body wash (sodium hypochlorite-based cleanser) for 3 months. When the patient returned after 3 months, the lesions, itch, and pigmentation had cleared (Figure 3).

DISCUSSION

CARP is relatively rare and has a poorly understood etiology. It has been theorized to be caused by bacterial colonization, specifically *Dietzia papillomatosis*, which has been found on the skin of affected individuals.[3] CARP also has a strong link to defects in keratinization. Other causes have been implicated but are less likely to be a primary driver of the disease. They include a reaction to UV light, endocrine abnormalities, *Malassezia* spp., and cutaneous amyloidosis.[3] Plaques or patches typically appear on the upper trunk and neck of affected individuals. Notably, CARP and acanthosis nigricans can appear similar on clinical examination, but they can be reliably differentiated through histopathologic analysis.[4]

Multiple therapeutic approaches have been explored for the treatment of CARP. Most commonly used are oral tetracyclines, particularly minocycline and doxycycline. One study assessing the effectiveness of oral minocycline and doxycycline for CARP reported that 60% of patients achieved complete clearance and 23% achieved partial clearance with a mean resolution period of 51.8 days.2 Other oral antibiotics, such as azithromycin and amoxicillin, have also been used.[2] Oral antibiotics are thought to be effective due to their dual anti-inflammatory and antimicrobial properties. Topical antibiotics have also been used to successfully treat CARP.[1]

CAB is a triple-combination topical gel currently indicated for the treatment of patients with acne vulgaris. It consists of 1.2% clindamycin phosphate, 0.15% adapalene, and 3.1% benzoyl peroxide.[5] The anti-infective properties of clindamycin phosphate, benzoyl peroxide, and hypochlorous acid may work synergistically to eliminate the bacterial component of the pathology, while adapalene and benzoyl peroxide help normalize keratinocyte turnover. Together, these may contribute to the resolution of pigmentary changes characteristic of CARP.

In this case study, the patient was initially prescribed oral doxycycline, topical minocycline, and topical ketoconazole concurrently, which did not clear the disease. After 3 months of using CAB and CLn body wash, the lesion was completely resolved. To our knowledge, this is the first case reported in the literature of a patient with CARP who was successfully treated with CAB and sodium hypochlorite-based body wash.

Topical clindamycin is an antibiotic that is indicated for treating acne vulgaris. It works by inhibiting protein synthesis by binding to 50S ribosomal subunits, thereby preventing the formation of peptide bonds.[6] Benzoyl peroxide is commonly utilized to prevent and treat acne by promoting bacterial protein degradation by generating free radicals; it also breaks down keratin and promotes dead skin cell shedding.[6] Its anti-infective plus keratolytic properties may have a role in resolving CARP. Sodium hypochlorite-based body wash, such as CLn body wash, provides additional antimicrobial action.[7] Adapalene modulates keratinocyte differentiation and reduces inflammation, contributing to the resolution of lesions and pruritus.[8]

Unlike oral antibiotics, which carry a risk of systemic side effects, CAB has no systemic side effects.[5] This can be advantageous for patients for whom oral antibiotics are contraindicated or poorly tolerated.

CONCLUSION

This case highlights the successful resolution of confluent and reticulated papillomatosis using topical clindamycin phosphate 1.2% / adapalene 0.15% / benzoyl peroxide 3.1% (CAB) gel in combination with a sodium hypochlorite–based body wash after failure of standard therapies. To our knowledge, this represents the first reported use of CAB gel for the treatment of CARP. This outcome supports the hypothesis that targeting both bacterial colonization and abnormal keratinization can be effective in refractory disease. CAB gel may offer a well-tolerated, non-systemic alternative for patients who do not respond to or cannot tolerate oral antibiotics. Further prospective studies are warranted to better define its role, durability of response, and optimal treatment duration in CARP.

DISCLOSURES

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Consent Statement: The authors obtained written consent from patients for their photographs and medical information to be published in print and online, and with the understanding that this information may be publicly available.

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BRIEF COMMUNICATION

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Minimum Margins After Positive Mohs Surgery Stages Correlate With Histologic Facing Loss

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INTRODUCTION

The appropriate size of surgical margins for stages after a positive Mohs micrographic surgery (MMS) stage has not been well studied. Proposed minimum peripheral margins (mPM) for excision can be determined using a mathematical model that describes the direct relationship between the extent of tissue block facing loss (FL) and the required mPM.

For Stage 1 MMS excisions, margins typically range from 2 to 3 mm, though they may vary from 1 mm to over 4 mm.[1,2]

Before the first tissue wafer is placed on a microscope slide during frozen section processing, tissue wafers are removed from the tissue block during the trimming or "facing" process. This FL discards a portion of the surgical margin. This may result in a deviation in position between the residual tumor's (RT's) actual location in the wound and the location where it is observed microscopically.

MATERIALS AND METHODS

The mathematical approach used to determine mPM was developed by Dr Sharon Tiefenbrunn (now deceased). It is based on the trigonometric formula used to calculate the unknown side of a right triangle when the length of one side (the amount of FL) and the angle of the hypotenuse (the angle of tumor spread with respect to the surgical margin) are known. The unknown side length is the mPM. (Figure 1)

Formula

$$\text{unknown side length (mPM)} = \frac{\text{(known side length (FL))}}{\text{(tangent of hypotenuse angle)}}$$

- A 180° arc encompasses all potential directions of RT extension. To ensure the subsequent stage excision encompasses RT, 95% of all potential angles and directions of RT extension should be included in the overlap of the RT focus. Including very shallow angles of tumor extension is not practical because angles less than 4.5 degrees result in an impractically larger calculation for mPM, and RT extension at extremely shallow angles to the surgical margin should be encompassed by the 95% calculated mPM.
- Assume 95% of RT extension is located within 95% of a 180° arc: 180° x 95% = 171°
- 180° - 171° = 9°
- 9° ÷ 2 = 4.5° is the 95% minimum angle of potential RT spread to each side of the tumor. This is the hypotenuse angle of the right triangle.
- The tangent of 4.5° = 0.079
- Therefore: mPM = FL/0.079

RESULTS

The authors calculated an FL of approximately 150 µm for their practices. In comparison, Taylor et al. reported FL values ranging from 187 µm to 338 µm.[3]

Using the formula above, the corresponding mPM values for FLs of 100 µm, 150 µm, 200 µm, 250 µm, 300 µm, and 350 µm are approximately 1.3 mm, 1.9 mm, 2.5 mm, 3.2 mm, 3.8 mm, and 4.4 mm, respectively. An mPM in the range of 1 to 4 mm would be appropriate, depending on the FL calculated by each MMS laboratory.

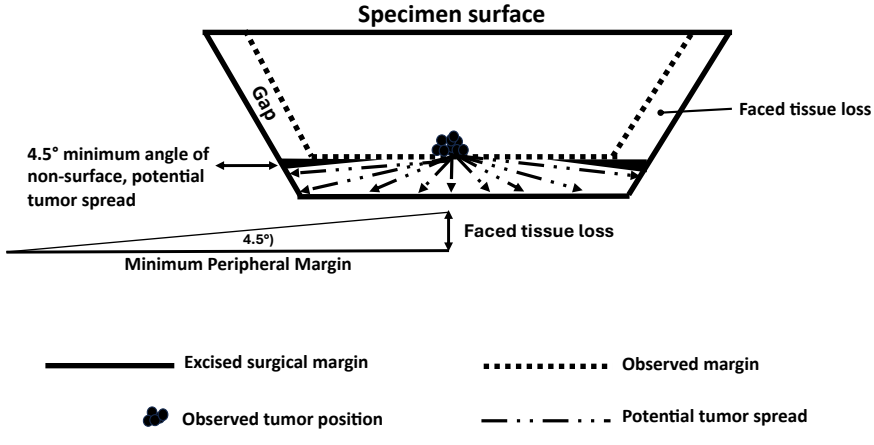
DISCUSSION

Before the first tissue wafer is placed on a microscope slide during MMS frozen section processing, multiple tissue wafers are removed from the tissue block during the trimming or "facing" process. This FL discards a portion of the true surgical margin. As a result, a deviation in position may exist between the RT's actual location in the wound and the location where it is observed microscopically (Figure 1).

Failing to consider this deviation between the observed and actual position of RT during the design of subsequent MMS stage excision margins may result in recurrences. A quantification of the relationship between FL and mPM would enhance both tumor control and normal tissue conservation during MMS.

The use of the mathematical formula for the tangent of a right triangle calculates an mPM that accounts for RT positional uncertainties created by FL.

FIGURE 1. Schematic representation of an excised Mohs surgical specimen before tissue flattening. A gap exists between the excised surgical margin and the microscopically observed margin following block facing. Using the formula described in the text, the minimum peripheral margin is calculated by dividing the faced tissue loss by the tangent of 4.5°. The minimum peripheral margin increases proportionally with the degree of facing tissue loss.



Several studies have reported that mPM for first-stage MMS excisions ranges from 1 mm to >4 mm.[1,2] However, there is a paucity of research addressing mPM in subsequent stages of MMS. Additionally, few studies have assessed the variability in FL among MMS laboratories.

Some MMS laboratories begin mounting tissue wafers on slides as soon as a minimal amount of tissue appears on the face of the tissue block, while others continue to trim the tissue block until a nearly complete tissue layer is exposed before placing the wafer on a microscope slide for examination by the Mohs surgeon. Based on FL considerations, the mathematical model presented suggests that the mPM for RT would typically range from 1 mm to 4 mm. Nonetheless, the use of margins under 2 mm for certain tumor types and anatomic sites may be oncologically inadvisable.

Jerrom and Varma[4] surveyed 39 Mohs surgeons and found considerable variability in the FL required to achieve full-margin visualization. FL ranged from less than 100 µm to 800 µm, with 59% of respondents achieving complete margin representation within 200 µm. A FL of 200 µm corresponds to a calculated mPM of 2.5 mm.

Mohs surgeons may readily calculate the amount of FL in their laboratory by multiplying the thickness of each tissue wafer by the number of wafers discarded after tissue is first encountered during block facing until the first wafer is mounted on a microscope slide. This calculated FL can then be used to adjust the estimated mPM using the formula described above. Notably, Taylor et al.[3] also demonstrated that the greater the FL, the more MMS stages were required to achieve clear margins.
In practical terms, the formula calculations suggest that an mPM of 2 mm to 4 mm for RT excisions will ensure that 95% of all potential directions of tumor infiltration are included, thereby minimizing the risk of false-negative results. A larger mPM may be appropriate for aggressive tumor subtypes and tumors that have exhibited widespread infiltration in previous stages. These findings also suggest that using less than 2 mm mPM for tissue conservation may be oncologically inadvisable.

DISCLOSURES

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This article is dedicated to the memory of our late colleague and teacher, Dr Sharon Tiefenbrunn, who developed the concept we present and championed mathematical precision in the practice of Mohs surgery.

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BRIEF COMMUNICATION

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Patients With Lichen Planopilaris are at Increased Risk of Skin Cancer

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INTRODUCTION

Patients with inflammatory alopecias face a potentially greater risk of cutaneous neoplasms in affected areas, likely due to chronic inflammation and reduced hair coverage.[1] While there have been isolated reports of scalp non-melanoma skin cancers (NMSC), particularly among women with lichen planopilaris (LPP), comprehensive evidence from large-scale studies is lacking.[2] To assess the risk for subsequent scalp NMSCs in LPP patients, we conducted a retrospective cohort study using data extracted from a global anonymized healthcare network (TriNetX Network, 2005-2025).

Three distinct alopecia cohorts were created, based on the specificity of ICD codes: LPP, androgenetic alopecia (AGA), and alopecia areata (AA), for comparative analysis.[3] Each alopecia cohort was matched with a healthy control for age, sex, race, and ethnicity. Odds ratios (OR) were calculated to evaluate risk for subsequent skin cancers, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma (MM), and melanoma in situ (MIS) (Tables 1 and 2).

Across all cohorts, women (LPP 72%, AA 60%, AGA 54%) and white patients were predominant (LPP 62%, AA 49%, AGA 62%; Table 1). Patients with LPP exhibited a significantly heightened likelihood of developing subsequent scalp and neck NMSCs (BCC: OR 2.03, CI 1.67-2.48; SCC: OR 2.03, CI 1.53-2.71) compared to controls (Table 2). LPP patients also had an increased risk of NMSC on all body sites, but no significant associations with MM or MIS. In comparison, patients with AA demonstrated modestly increased risks for SCC, while those with AGA showed a lower risk specifically for scalp and neck BCC. Interestingly, both the AA and AGA cohorts demonstrated protective effects against MM/MIS overall, not mirrored in the LPP cohort.

These findings suggest an association between LPP and increased risk of subsequent NMSCs, which was not observed in the AA and AGA cohorts. We could not verify the clinical observation that NMSCs predominantly manifest in affected scalp areas, primarily due to constraints imposed by the ICD code merging "neck and scalp" into a singular anatomical

TABLE 1.

Patient Demographic Information for Lichen Planopilaris, Alopecia Areata, and Androgenetic Alopecia Cohorts[a]

	LPP (n=42,459)	AA (n=101,650)	AGA (n=102,273)
Age, mean (SD) years	57 (16)	33 (21)	46 (18)
Gender, no (%)			
Female	30,625 (72)	61,235 (60)	54,894 (54)
Male	10, 047 (24)	37,971 (37)	44,308 (43)
Race, no (%)			
White	26,182 (62)	49,670 (49)	62,967 (62)
Black/African American	5,020 (12)	14,401 (14)	8,163 (8)
Asian	2,360 (6)	6,724 (7)	6,790 (7)
Other	1,298 (3)	6,518 (6)	5,378 (5)
Unknown	7,269 (17)	23,212 (23)	17,877 (17)
Ethnicity, no (%)			
Not Hispanic or Latino	29,254 (69)	57,659 (57)	66,109 (64)
Hispanic or Latino	2,223 (5)	15,481 (15)	7,373 (7)
Unknown	10,982 (26)	28,510 (28)	28,791 (28)

Abbreviations: AA, alopecia areata; AGA, androgenetic alopecia; LPP, lichen planopilaris; no, number of patients; SD, standard deviation.
ICD 10 codes for alopecias are as follow: LPP = L66.1; AA = L63; AGA = L64.
[a]The discrepancy in cohort sizes reflects the relative prevalence of each alopecia subtype in the general population, as well as the nature of real-world data acquisition through the TriNetX.

TABLE 2.

Skin Cancer Risk in Patients With Lichen Planopilaris, Alopecia Areata, and Androgenetic Alopecia After Propensity Score Matching

Skin Cancer Type	LPP (n=42,459)	AA (n=101,650)	AGA (n=102,273)
BCC, overall	1.53* (1.41-1.66)	0.97 (0.88-1.06)	0.97 (0.91-1.04)
Scalp and Neck BCC	2.03* (1.67-2.48)	1.03 (0.81-1.32)	1.27* (1.07-1.51)
SCC, overall	1.76* (1.59-1.94)	1.21* (1.07-1.38)	0.83* (0.75-0.91)
Scalp and Neck SCC	2.03* (1.53-2.71)	1.50* (1.06-2.12)	0.99 (0.77-1.28)
MM, overall	1.04 (0.87-1.25)	0.64* (0.53-0.78)	0.58* (0.50-0.68)
Scalp and Neck Malignant Melanoma	1.04 (0.60-1.83)	1.17 (0.54-2.52)	0.70 (0.41-1.19)
MIS, overall	1.12 (0.93-1.36)	0.65* (0.53-0.81)	0.71* (0.60-0.84)
Scalp and Neck MIS	1.59 (0.87-2.92)	1.2 (0.52-2.78)	1.48 (0.85-2.57)

*Indicates statistical significance against age, sex, race, and ethnicity matched control cohort.
Abbreviations: AA, alopecia areata; AGA, androgenetic alopecia; BCC, basal cell carcinoma; CI, confidence interval; LP, lichen planus; LPP, lichen planopilaris; MIS, melanoma in situ; MM, malignant melanoma; n, number of patients; OR, odds ratio; SCC, squamous cell carcinoma.
Odds ratios were calculated for the development of each skin cancer outcome following a previous diagnosis of LPP, AA, or AGA for each separate case cohort compared to its respective healthy control cohort. These values were adjusted for multiple hypothesis testing using the false discovery rate adjustment method.
ICD codes for diagnoses of skin cancers are as follow: LPP = L66.1; AA = L63; AGA = L64; Overall BCC: C44.01, C44.11, C44.21, C44.31, C44.41, C44.51, C44.61, C44.71, C44.81, C44.91; Scalp and Neck BCC = C44.41; Overall SCC = C44.02, C44.12, C44.22, C44.32, C44.42, C44.52, C44.62, C44.72, C44.82, C44.92; Scalp and Neck SCC = C44.42; Overall MM= C43; Scalp and Neck MM = C43.4; Overall MIS = D03; Scalp and Neck MIS = D03.4.

category. Nevertheless, the data not only highlights an elevated risk for NMSCs on the scalp and neck but also overall in LPP patients. Due to the limitations of the dataset, we were unable to collect information on confounding variables such as environmental risk factors, frequency of dermatologic visits, concomitant medications, or Fitzpatrick skin types (though race was a criterion for cohort matching). Future research will serve to elucidate whether this heightened risk is from the inflammatory processes inherent in LPP, such as IL17, or an unintended effect of therapy, primarily local and/or systemic immunomodulators.[4,5] In a separate parallel analysis of patients with lichen planus, we observed a similar elevated risk of NMSCs (overall BCC: OR 1.21, CI 1.14-1.28; overall SCC: OR 1.68, CI 1.57-1.79; scalp/neck BCC: OR 1.78. CI 1.55-2.03; scalp/neck SCC: OR 1.73 CI 1.46-2.05), reinforcing the broader oncologic risk associated with lichenoid inflammatory diseases. We advise dermatology providers to have heightened acuity for cutaneous malignancies in patients with LPP, particularly in the scalp.

DISCLOSURES

The authors have no conflicts of interest to declare.

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BRIEF COMMUNICATION

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Dermatologists' Practices and Perspectives on Human Papillomavirus Surgical Plume, and Cancer Risk

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INTRODUCTION

This is the first study to examine Human Papillomavirus (HPV) vaccination rates, protective equipment use, and self-reported health outcomes among dermatologic surgeons in the context of surgical plume exposure. Dermatologists routinely perform electrocautery and laser procedures that generate a surgical plume—a bioaerosol containing toxic chemicals, cellular debris, and viral particles such as human papillomavirus (HPV) DNA.[1,2]The presence of HPV DNA in the surgical plume raises concerns about occupational exposure and associated malignancies.[2,3] Although smoke evacuators are recommended, protective practices among dermatologists remain inconsistent, and institutional policies vary widely. While HPV vaccination offers protection against HPV-related cancers, the vaccination rate among dermatologists is not well characterized. Our study aimed to assess HPV vaccination status, awareness of plume-related hazards, use of protective measures, and self-reported health outcomes among dermatologists. Findings may inform occupational safety guidance and highlight current gaps in protection practices.

We conducted an IRB-exempt, cross-sectional survey of 300 board-certified dermatologists, residents, and fellows affiliated with the Florida Academy of Dermatology from April to June 2025. A total of 62 responses were collected anonymously (21% response rate) using a 30-item, study-specific questionnaire administered via Google Forms. The survey assessed the frequency of plume-generating procedures, use of protective equipment, HPV vaccination status, prior training on plume safety, self-reported symptoms, and perceived barriers to implementing safer practices.

Among respondents, 84% reported using electrocautery or CO_2 laser daily or more often. Despite this frequent exposure, 65% lacked access to or never used smoke evacuators, and only 16% reported consistent use during laser procedures. Institutional mandates were rare (8%). While 74% were aware that HPV DNA can be present in the surgical plume and 69% perceived a moderate or significant transmission risk, only 8% consistently used N95 respirators when treating HPV-positive lesions. The most commonly used protective equipment included surgical masks (n=42), face shields or goggles (n=19), and local exhaust ventilation (n=9); notably, 11 respondents reported using no protective measures at all. Reported barriers included equipment cost (n=24), lack of awareness (n=17), lack of institutional support (n=16), and resistance to change (n=11); 10 respondents reported no barriers.

To examine whether clinical experience influenced risk perception, a chi-square test compared years in practice with perceived risk of HPV transmission via surgical plume. The association was statistically significant ($\chi^2(9) = 17.77$, $P=0.038$), suggesting that experience affects how dermatologists assess plume-related risks—but not in a linear fashion. More experienced dermatologists showed greater polarization: some perceived high risk, others no risk, potentially reflecting varying personal experiences. These findings underscore the need for standardized, evidence-based education across all stages of training.

HPV vaccination coverage was mixed: 47% were fully vaccinated, 29% had never received the vaccine, and 18% were above the recommended age range. Among unvaccinated respondents, 44% said they would be very likely to receive a booster if recommended, suggesting openness to protective measures when framed as occupational risk mitigation. Open-text responses revealed confusion regarding vaccine eligibility for providers over age 45, highlighting the need for clearer occupational guidance.

Formal training on plume safety was limited, with 58% reporting no prior instruction within the last five years. While ten early-career dermatologists lacked formal education on this topic, the majority without training were more experienced (n=26 with 11+ years, including n=18 with 21+ years in practice), suggesting that gaps are more prevalent among seasoned clinicians due to evolving safety standards.

Nine respondents reported symptoms they suspected were related to plume exposure, including throat irritation (n=6), nasal congestion or sinusitis (n=5), eye irritation (n=2),

headaches (n=2), chronic cough (n=1), and nausea (n=1). All symptomatic individuals reported daily exposure to plume-generating procedures. Meanwhile, 51 respondents reported no symptoms. Notably, 37% (n=23) reported knowing at least one colleague diagnosed with head and neck squamous cell carcinoma (HNSCC). Given the general population incidence of approximately 11 per 100,000 per year,[4] this observation may point to a disproportionate occupational burden among dermatologic surgeons and warrants further investigation. Encouragingly, 81% expressed interest in additional education or research on plume safety.

Our findings reveal a disconnect between procedural exposure and consistent protective practices among dermatologists. Despite awareness of HPV transmission risk, safety behaviors remain inconsistent due to systemic barriers, limited training, and unclear vaccination guidance. While limited by the cross-sectional design, modest response rate, and potential self-report bias, the results underscore the need for improved education, institutional support, and updated clinical guidelines. Future studies with broader participation and longitudinal follow-up are warranted to better assess causality and define occupational risk.

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BRIEF COMMUNICATION

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Time is Tissue: A Representative Case Report Highlighting the Importance of Early Clinical Diagnosis of Necrotizing Fasciitis

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INTRODUCTION

Necrotizing fasciitis is an uncommon but potentially rapidly fatal infection. The mortality rate is estimated to be 23–29%[1] and when it affects the limbs, the amputation rate is 11–14%.[1] There are 4 types of necrotizing fasciitis: Type 1 (polymicrobial in immunocompromised patients), type 2 (group A streptococcus [GAS] in healthy people), type 3 (gas gangrene due to clostridium), and type 4 (marine organisms and fungal infections). Notably, necrotizing fasciitis type 2 (NF2) associated with GAS is associated with septic shock and multiorgan failure, and therefore, early recognition and treatment are critical to a good prognosis.[2] Delays in diagnosis are unfortunately common due to the nonspecific nature of cutaneous signs and symptoms, radiological findings that lag behind the progressive and extensive soft tissue destruction, and the low frequency with which first responders and primary care and emergency medicine physicians encounter this entity.[3,4]

We report a case of NF2 that firstly benefited from early diagnosis and treatment, which resulted in a favorable outcome, and secondly demonstrated unexpected oral antibiotic failure due to a GAS M-protein variant.

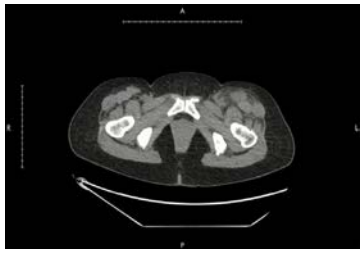
Case Report

A previously healthy 50-year-old woman presented to the emergency room with severe pain in her left thigh for 4 days, limited weight-bearing capacity, and associated fever, fatigue, general body aches, and diarrhea. The patient did not report a history of injury to the affected area, nor any observed visible changes prior to presentation. Recent past medical history was pertinent for tonsillitis approximately 10 days preceding the leg pain, empirically treated with a 7-day course of amoxicillin/clavulanate potassium. There was no microbiological confirmation of GAS with a throat swab. The patient did not report any other new medications nor any history of illicit drug use. The patient did not report any other new medications nor any history of illicit drug use.

FIGURE 1. Left thigh with minimal cutaneous changes on day 1 before the operation.

On examination, the left leg revealed minimal erythema (Figure 1) and was exquisitely tender to palpation on the medial aspect of the left thigh. The patient was initially normotensive on arrival, but suddenly developed tachycardia (120 bpm) and hypotension (79/50 mmHg). Initial labs revealed white cell count to be 17.1 K/UL and serum creatinine to be 4.6 mg/dL, though the blood cultures were negative. The presumed diagnosis was acute renal failure associated with sepsis of unknown origin, though the disproportionate soft tissue pain raised the possibility of necrotizing fasciitis. Broad-spectrum antibiotics, including vancomycin, piperacillin-tazobactam, and clindamycin were initiated. Ultrasound of the left thigh was within normal limits, and a CT scan demonstrated soft tissue edema in the anterior aspect of her left thigh (Figure 2). Surgical exploration of her thigh revealed edema localized to the sartorius muscle with no

FIGURE 2. CT scan – Left thigh on presentation with edema, no other signs of necrotizing fasciitis.



evidence of necrosis. The diagnosis of early necrotizing fasciitis was confirmed. The area was lavaged, and cultures of the site were taken, which eventually grew GAS sensitive to penicillin and cephalosporins. The wounds were left open to drain and heal by secondary intention. The patient continued to improve with IV antibiotics and was discharged with oral cefuroxime.

However, six days after discharge, the patient noticed a recurrence of the pain in her left thigh and was re-admitted. Intravenous vancomycin, clindamycin, and piperacillin-tazobactam were initiated. Repeat cultures and sensitivities in this admission confirmed GAS sensitivity to cefuroxime, which the patient took prior to this administration. The failure of the cefuroxime was ultimately attributed to GAS with a highly virulent antigenic variant M-protein. She was discharged on an additional 4 weeks of high-dose IV ceftriaxone 2 g BD and oral linezolid. On follow-up after the 4 weeks of home therapy, the episode resolved, and she continues to remain well at the time of this report.

DISCUSSION

This case highlights the importance of early diagnosis and rapid institution of broad-spectrum antibiotics to ensure a successful outcome in necrotizing fasciitis. Front-line physicians in primary care and emergency rooms need to have a high index of suspicion because the absence of clinical and diagnostic signs in the early stage of the disease can make the diagnosis difficult.[5] Investigations, such as bedside ultrasound and CT scan, can also be negative for classic signs of necrotizing fasciitis in the early stages of disease.[6] Ultimately, surgical exploration will reveal the diagnosis.

Another important issue highlighted by this case report is the potential role of the hypervariable GAS M-protein in antibiotic treatment failure. The M-protein is a surface protein of GAS that is normally attached to the cell wall. It is the key virulence factor that helps the bacteria survive in human tissues and fluids primarily by preventing phagocytosis by polymorphonuclear leukocytes, allowing the GAS bacteria to persist in infected tissues. As there are over 200 serotypes, this can lead to variable efficiency of the GAS in evading the host's immune defences.[7]

In this case, the infection responded to high-dose broad-spectrum intravenous antibiotics. However, on two occasions, there was failure of oral antibiotics to fully eradicate all the GAS bacteria, leading to the initial episode of necrotizing fasciitis following tonsillitis and the flare of the infection after the first hospital discharge. Although M-protein mutation testing was not performed, it was presumed that the GAS had an antigenic variation of M-protein, which was extremely efficient in evading host immune cell phagocytosis, given the patient had no history of immunodeficiency. Therefore, the successful treatment strategy in this case was to utilize high-dose intravenous antibiotics for a prolonged period. Other potential treatment options being investigated currently include a vaccine to the M-protein[8] and intravenous immunoglobulins.[9]

CONCLUSION

Recognizing and having a high index of suspicion of necrotizing fasciitis in the setting of febrile illness and disproportionate soft tissue pain is critical as clinical and radiological signs may be absent at this early stage. Given the rapid fulminant course of this infection, early diagnosis and intervention are key to achieving a positive outcome. Furthermore, the possibility of a highly virulent M-protein variant GAS bacteria should be considered in the setting of antibiotic treatment failure with a sensitive pathogen, and to institute prolonged high-dose antimicrobial therapy.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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Journal of Drugs in Dermatology

Chronic Kidney Disease and Postoperative Complications Following Mohs Surgery: A Retrospective Cohort Study

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To the Editor,

Chronic kidney disease (CKD) affects approximately 14% of adults nationally and is characterized by impaired immunity, systemic inflammation, and microvascular dysfunction.[1,2] These physiologic disruptions impair wound healing and predispose patients to adverse surgical outcomes.[1,2] Mohs micrographic surgery (MMS) is the gold standard for managing nonmelanoma skin cancer (NMSC), offering high cure rates while preserving healthy tissue.[3] Given that MMS is frequently performed in medically complex patients,[3] including those with CKD, understanding the postoperative risks in this population is critical. While CKD has been broadly linked to poor surgical outcomes,[2] limited data exist on its impact on complication rates following MMS.

A retrospective cohort study was conducted using the TriNetX Research Network to evaluate the risk of postoperative complications in patients with CKD undergoing MMS for NMSC. Adults diagnosed with basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) who underwent MMS between July 21, 2020, and July 21, 2025, were identified. Patients with CKD were identified using the International Classification of Diseases, 10th revision code (ICD-10-CM) for CKD (N18). Patients with inherited or acquired disorders that impair wound healing, systemic infection, or sepsis on the day of surgery, or documentation of previous postoperative complications were excluded. A comparator cohort of patients without CKD was generated using 1:1 propensity score matching on age, sex, race, ethnicity, immunosuppressant medication use, and relevant comorbidities, including obesity, smoking, diabetes mellitus, chronic venous insufficiency, and peripheral arterial disease. The final matched cohorts included 25,016 patients each. Postoperative outcomes were assessed at 30-days and 90-days after surgery with risk ratios (RR). Statistical significance was defined as a two-sided *P*-value <0.05.

TABLE 1.

Risk of Postoperative Complications 30 Days and 90 Days Following Mohs Micrographic Surgery for Nonmelanoma Skin Cancer in Patients Diagnosed With Chronic Kidney Disease (CKD)

Outcomes	CKD Cohort	No CKD Cohort	Risk Ratio (95% Confidence Interval)	*P*-value	CKD Cohort	No CKD Cohort	Risk Ratio (95% Confidence Interval)	*P*-value
	Number of eligible individuals (number of outcomes, 30 days)	Number of eligible individuals (number of outcomes, 30 days)			Number of eligible individuals (number of outcomes, 90 days)	Number of eligible individuals (number of outcomes, 90 days)		
Postoperative Infection	24048 (127)	24405 (100)	1.29 (1.01-1.67)	0.047	24048 (162)	24405 (125)	1.32 (1.04-1.66)	0.021
Delayed wound healing	24328 (59)	24594 (44)	1.36 (0.92-2.00)	0.11	24328 (134)	24594 (94)	1.44 (1.11-1.88)	0.0062
Dehiscence	24540 (58)	24704 (36)	1.61 (1.07-2.46)	0.019	24540 (132)	24704 (95)	1.4 (1.08-1.82)	0.012
Graft complications	24931 (14)	24964 (≤10)	1.5 (0.67-3.60)	0.32	24931 (37)	24964 (17)	2.18 (1.23-3.87)	0.0077

By 30 days postoperatively, patients with CKD experienced significantly higher rates of surgical site infections (RR 1.29, *P*=0.047) and wound dehiscence (RR 1.61, *P*=0.019; Table 1). By 90 days, additional complications emerged: the risks of delayed wound healing (RR 1.44, *P*=0.0062) and graft complications (RR 2.18, *P*=0.0077), observed only among patients whose wounds were repaired with grafts, were now significantly increased. Further, significantly elevated risks of postoperative infection (RR 1.32, *P*=0.021) and dehiscence (RR 1.40, *P*=0.012) persisted.

These findings suggest CKD is an independent risk factor for adverse outcomes following MMS. Complications appear to follow a biphasic pattern: acute complications such as infection and dehiscence are more prevalent early, while delayed wound healing complications emerge later. These trends may reflect the progressive tissue repair impairment seen in CKD, where uremia, vascular dysfunction, and chronic inflammation impair healing.[4] Dermatologic surgeons are encouraged to recognize CKD as a contributor to impaired healing following MMS, counsel patients accordingly during preoperative assessments, and anticipate and readily manage complications. Limitations include reliance on ICD-10-CM coding, retrospective design, and lack of clinical information on perioperative antibiotic use, defect size, or repair type. Future studies should incorporate prospective clinical data to definitively evaluate causality and guide targeted perioperative management.

DISCLOSURES

Dr Tolkachjov is a speaker/investigator for CASTLE Biosciences, Bioventus, Kerecis, Leo Pharma, StimLabs, Regeneron, and Boehringer Ingelheim. All authors have no relevant conflicts of interest to disclose.

Ethics Approval/Ethical Statement: Data accessible via TriNetX is presented in aggregate form and only contains anonymized data as per the deidentification standard defined by the US Health Insurance Portability and Accountability Act (HIPAA) in section 164,514(a). Given that this study used only de-identified data and did not involve individually identifiable patient data, this study was exempt from Institutional Review Board Approval.

Data Sharing Statement: The data that support the findings of this study were obtained from the TriNetX Research Network and are available to other researchers upon request and with appropriate access permissions. De-identified aggregate-level data, a data dictionary describing the variables used, and the statistical code used for cohort creation and outcome assessment can be shared upon reasonable request to the corresponding author. Data access requires institutional credentials or collaboration with an institution that maintains a TriNetX license. Analyses may be replicated or extended within the TriNetX platform. There are no additional restrictions on the use of the shared materials beyond those imposed by the TriNetX user agreement.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Benzoyl Peroxide and Malignancy Risk: A Systematic Review and Meta-analysis of Over 4 Million Patients

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Dear Editor,

Benzoyl peroxide (BPO) is a widely used agent in the treatment of acne vulgaris (AV). Recently, concerns have emerged regarding the safety of BPO products, as they have been reported to degrade into benzene, particularly when exposed to elevated temperatures (37°C). Benzene exposure has been associated with an increased risk of several malignancies, particularly hematologic malignancies and internal malignancies, especially lung cancer.[1,2] Given the critical role of BPO in acne management and the potential safety concerns, we conducted a systematic review and meta-analysis to evaluate the association between BPO use for acne and the risk of developing malignancies.

A systematic search was conducted in PubMed, Embase, and Web of Science following PRISMA guidelines.[3] Inclusion criteria were: (1) Human participants with a diagnosis of AV or who were using BPO; (2) A clearly defined comparator group not exposed to BPO (eg, acne patients without BPO use, or non-acne controls). The search strategy was ('Benzoyl peroxide' OR BPO) AND ('hematologic malignancies' OR 'hematologic malignancy' OR 'blood cancer' OR leukemia OR lymphoma OR 'multiple myeloma' OR 'myelodysplastic syndrome' OR 'lung cancer'). Statistical analyses were performed using R version 4.3.2. A random-effects model was performed to determine the proportion with a 95% confidence interval (CI). Heterogeneity was assessed using the I^2 statistic.

Four studies were included (1, 2, 4, 5), encompassing a total of 4,062,218 patients. Three of these studies reported baseline characteristics; among them, the mean age was 20.3 years, 64.1% were female, and 63.0% were White. Additional baseline characteristics are presented in Table 1. Risk of leukemia was reported in all studies, and the pooled analysis (Figure 1A) showed no statistically significant association between patients using BPO and those who were not (RR 0.91; 95% CI 0.68, 1.21; P=0.5; I^2 = 69.7%). Three studies specifically reported on the risk of acute myeloid leukemia (AML), and the pooled analysis (Figure 1B) also did not demonstrate a statistically significant difference between the two groups (RR 0.98; 95% CI 0.67, 1.43; P=0.9; I^2 = 77.3%). Two studies reported on the risk of lymphoma (Figure 1C) and any hematologic malignancy (Figure 1D); neither analysis showed a statistically significant increase in risk, lymphoma (RR 0.99; 95% CI 0.70, 1.41; P=0.9; I^2=79.0%) and any hematologic malignancy (RR 0.99; 95% CI 0.92, 1.06; P=0.7; I^2 = 0%). Internal malignancy was reported by one study, which also found no significant difference in risk between BPO users and non-users. One study reported the risk of lung cancer, likewise finding no statistically significant difference.

Our pooled analyses of more than four million patients consistently demonstrated no statistically significant association between BPO use and the risk of leukemia, acute myeloid leukemia, lymphoma, or any hematologic malignancies. These results suggest no significant association between BPO use and malignancy risk.

TABLE 1.

Baseline Characteristics of Included Studies

Study	Study design	Patients, n	Age at index, y§	Female, %	White, %	Hispanic or latino, %	Tobacco use, %	Alcohol, %
CHAN 2024	Retrospective cohort	410,997‡ 410,997†	22.2 (11.6)‡ 22.1 (11.7 †	63.1‡ 63.0†	52.5‡ 52.7†	14.1‡ 14.2†	N/A	N/A
GARATE 2024	Retrospective cohort	91,055‡ 91,055†	22.24 (7.4)‡ 22.25 (7.5)†	61.8‡ 62.4†	65.8‡ 66.6†	9.1‡ 8.6†	1.6‡ 1.7†	0.4‡ 0.4†
VEENSTRA 2024	Cross-sectional analysis	668,756‡ 1,583,316†	N/A	N/A	N/A	N/A	N/A	N/A
VEENSTRA 2025	Retrospective cohort	115,257‡ 690,785†	18.4 (5.0)‡ 18.1 (5.0)†	65.5‡ 65.7†	72.0‡ 73.0†	9.9‡ 9.5†	13‡ 12.3†	4.1‡ 3.8†

‡ Intervention; † Control; § Mean (SD).

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FIGURE 1A. Forest plot on risk of leukemia.

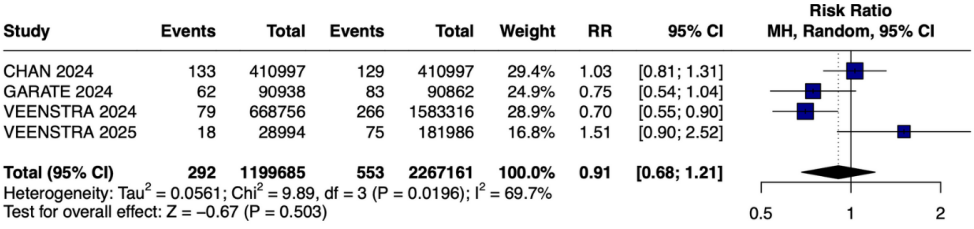


FIGURE 1B. Forest plot on risk of acute myeloid leukemia.

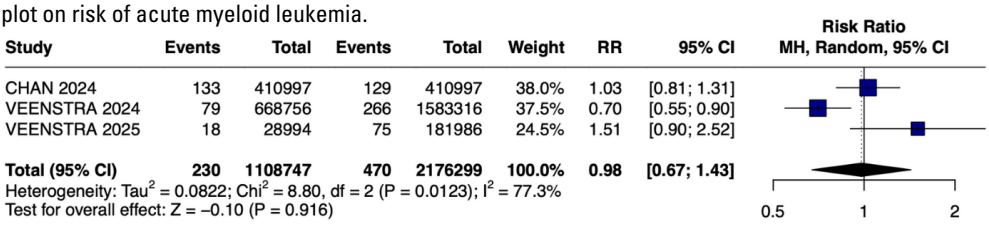


FIGURE 1C. Forest plot on risk of lymphoma.

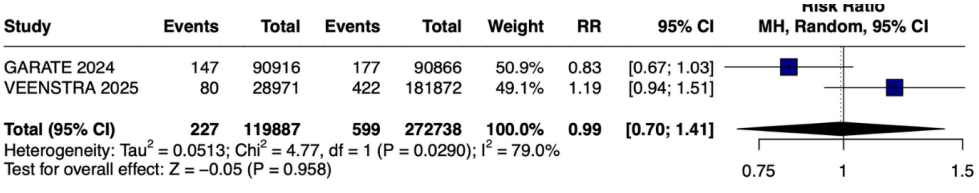
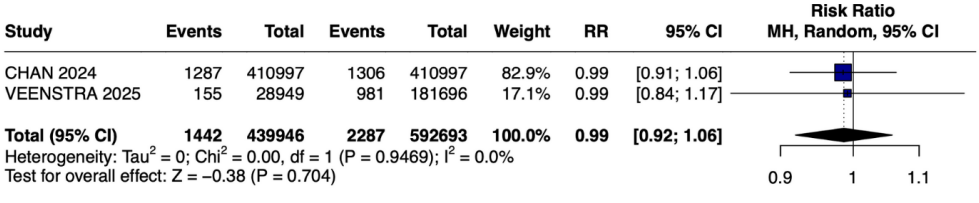


FIGURE 1D. Forest plot on risk of any hematologic malignancy.



Recent commentaries, such as that by Del Rosso,[6] have emphasized the uncertainty and 'many unanswered questions' surrounding benzoyl peroxide's safety profile in the context of benzene formation. Our findings are in line with those of Czyz et al[7] reported that despite raising concerns about benzene formation, they likewise concluded that available evidence does not support an elevated risk of hematologic malignancies with BPO use in pediatric populations. Study limitations include potential exposure misclassification due to reliance on prescription records or diagnostic codes and insufficient detailed exposure data (dosage, duration, cumulative use) across studies, hindering dose-response analysis.

Our findings suggest that the use of BPO for acne does not significantly increase the risk of benzene-related cancers

DISCLOSURES

The authors have no conflicts of interest or financial relationships to disclose relevant to the content of this article.

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Thermal Imaging for Cryotherapy Documentation in Dermatology Practice

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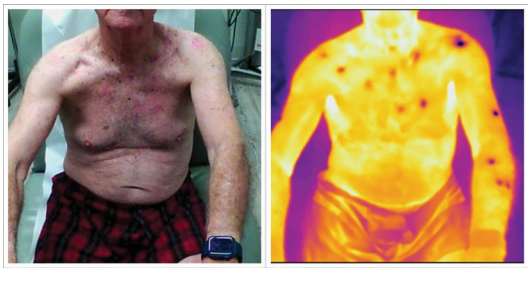
To the Editor,

Liquid Nitrogen (LN_2) is one of the most common dermatologic procedures performed by dermatologists and other physicians. Actinic keratoses (AK), seborrheic keratoses (SK), and warts are the most common lesions treated with LN_2. The 2023 CMS data and research statistics listed code 17110, destruction of benign lesions up to 14, and code 17000, destruction of premalignant lesions 1st, in the top 200 billed codes. Allowed services totaled 3,037,446 for code 17110 and 6,114,068 for code 17000 in 2023.[1]

To administer LN_2, providers typically will hold a cryocanister in one hand while feeling for skin lesions with the other hand. Dermatologists often treat between 1 and 50 or more distinct sites per encounter, and scribes are often used to record the location, number, and diagnosis of each lesion. This current workflow inefficiency is associated with rapidly increasing labor costs and declining reimbursement. Without a scribe, providers rely on recall to document LN_2 treatments. Visible cameras, as well as ambient artificial intelligence (AI) audio scribes, are of limited use in cryotherapy because they cannot accurately capture the locations of LN_2-treated lesions (Figure 1). AI-scribes fail to address the practical needs of dermatology providers who spend a large portion of their visits administering LN_2. We report a novel solution that enables providers to perform and document liquid nitrogen simultaneously.

FIGURE 1. SK photographed 3 seconds after treatment (not visible).

FIGURE 2. Visible and corresponding thermal images of multiple AK lesions photographed 3 seconds after treatment.



The Technique

While visible imaging cannot capture LN2-treatment sites, thermal imaging can capture cryotherapy sites with precision (Figure 2). Cryotherapy-treated lesions appear as foci of cooler temperatures on thermal imaging and undergo temporal decay as they warm. When treating an AK for 10 seconds with a 1–2 mm rim of LN2, the AK will be visible on thermal imaging for approximately 1 minute after treatment.

We have developed a HIPAA-compliant solution that utilizes a lightweight adapter to attach an Android device with integrated visible and FLIR Lepton 3.5 thermal cameras to a cryocanister (Figure 3). After treating a region of lesions with LN_2, the provider can quickly tap the camera screen, capturing visible and thermal images of the area. These images are processed via an advanced machine learning (ML) pipeline for automated treatment site detection and anatomical mapping. The provider can quick-select diagnoses, tag lesions to observe, and download a summary report that allows for electronic medical record (EMR) integration (Figure 4).

Practical Implications

Thermal imaging has been used to assess skin conditions, including psoriasis, skin cancers, burns, and cosmetic treatments such as cryolipolysis.[2] To date, there are no reports on the use of thermal imaging for documentation of cryotherapy treatment sites. With current off-the-shelf thermal cameras, providers are unable to administer LN_2 and subsequently operate a thermal camera quickly enough before treated lesions become undetectable. Incorporation of this novel thermal imaging

FIGURE 3. The adapter and thermal camera attached to the cryocanister, and the provider performing cryotherapy while capturing

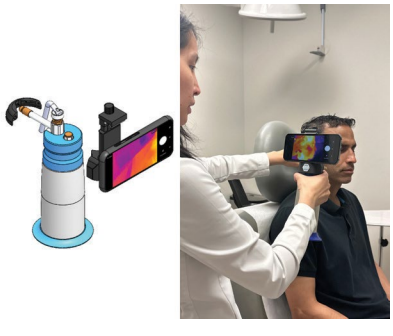


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FIGURE 4. The downloadable treatment summary with corresponding composite diagram.

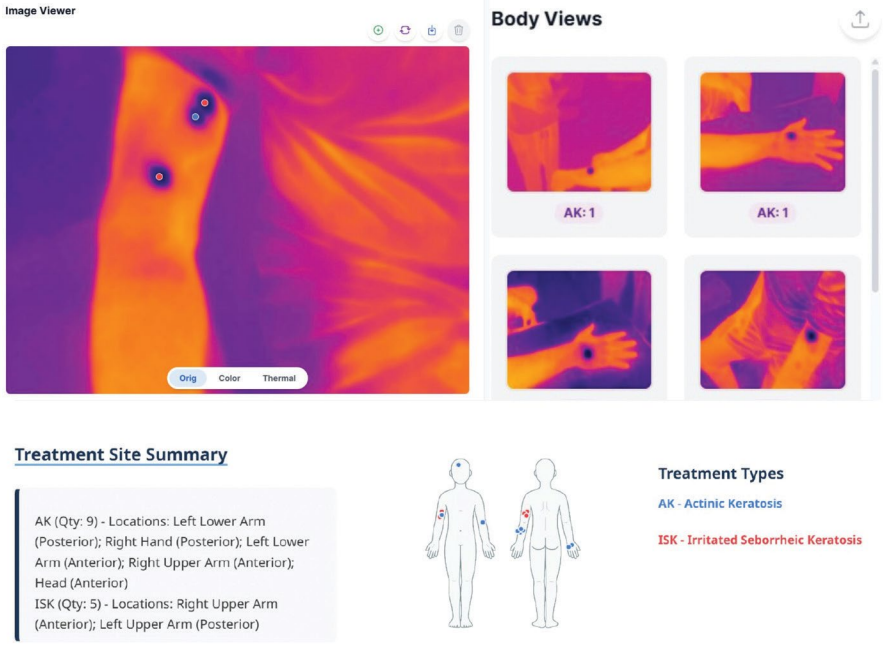
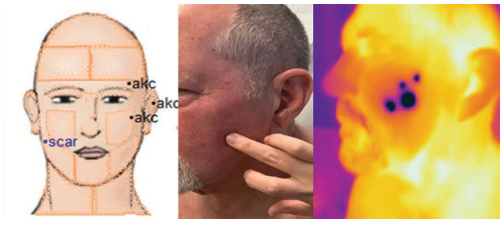


FIGURE 5. An EMR diagram showing a lack of specificity with manual cryotherapy charting, a visible image of an AK re-treated at multiple visits due to unclear charting, and a thermal image showing the precise location of treated sites.



technique into our charting will allow a provider to perform and document LN2 procedures independently and reduce labor costs.

With our current charting tools, providers may unknowingly re-treat the same lesions with LN2 multiple times because the exact location of prior treatment sites could not be precisely recorded (Figure 5). Patient care will be improved because lesions that failed LN_2 can now be readily identified. As a low-cost solution, this novel technique efficiently captures the visual information needed to document LN_2 and fills a much-needed gap that current AI Scribes and dermatology-specific EMRs lack. Future studies will explore the diagnostic uses of thermal imaging after liquid nitrogen treatment in dermatology.

DISCLOSURES

Katherine B. Lee MD, has a patent pending for CryoCaptures. Dr Lee received an honorarium from the American Academy of Dermatology for CryoCaptures being named the 2025 Innovation Academy Derm Tank winner.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Malignancy Risk in Autoimmune Blistering Disorders: A Retrospective Cohort Study

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To the Editor,

Autoimmune blistering disorders (AIBD) are chronic, antibody-mediated diseases of the skin and mucous membranes that carry substantial morbidity and mortality.[1,2] Previous studies have suggested an association with malignancy, particularly squamous cell carcinoma and lymphoma, but have been limited by small sample sizes and subtype-specific cohorts.[3] We conducted a population-based analysis using the TriNetX Research Network, a federated electronic health record database, to better define malignancy risk in this population.

We conducted a retrospective cohort study using the TriNetX Research Network, a de-identified EHR database with longitudinal patient-level data from over 100 healthcare organizations. We identified adults with ICD-10 codes for pemphigus (L10), pemphigoid (L12), or other bullous disorders (L13) and excluded those with prior malignancy. The index date was the diagnosis of bullous disorder for our exposure cohort and a general exam encounter for controls; events >20 years prior were excluded. Patients were matched 1:1 to controls by demographics (age, sex, race), comorbidities (hypertension, diabetes, chronic respiratory disease, obesity, ischemic heart disease, chronic kidney disease, liver disease, heart failure, and nicotine dependence), family history of malignancy, and immunosuppression use, yielding 30,218 patients per group. Outcomes were assessed from one day post-index through 1, 5, and 10 years of follow up. Covariate balance was assessed via standardized mean differences, with all covariates achieving SMD <0.1. Absolute risks, risk differences (RD), Kaplan-Meier

TABLE 1.

Hazard Ratios With 95% Confidence Intervals For Malignancies In Aibd Vs Controls at 1, 5, and 10 Years.

Malignancy	1 Year HR (95% CI)	5 Year HR (95% CI)	10 Year HR (95% CI)
Any neoplasm	5.607 (5.093, 6.174)	3.595 (3.416, 3.784)	3.275 (3.13, 3.426)
Any malignant cancer	4.478 (3.768, 5.322)	3.066 (2.808, 3.348)	2.734 (2.531, 2.953)
Any lymphoma	15.851 (5.736, 43.8)	4.376 (2.979, 6.428)	3.472 (2.51, 4.804)
Non-Hodgkin lymphoma	19.897 (6.205, 63.8)	4.314 (2.882, 6.457)	3.344 (2.389, 4.681)
Squamous cell carcinoma of skin (SCC)	16.727 (8.156, 34.304)	7.565 (5.659, 10.112)	6.523 (5.081, 8.373)
Basal cell carcinoma of skin (BCC)	12.958 (7.167, 23.427)	4.95 (3.972, 6.167)	4.909 (4.04, 5.964)
Any melanoma	15.596 (4.814, 50.529)	4.134 (2.805, 6.094)	3.793 (2.684, 5.362)
Melanoma in situ	--*	5.374 (2.925, 9.874)	4.1 (2.498, 6.727)
Malignant melanoma	11.784 (3.589, 38.691)	5.027 (3.102, 8.147)	3.905 (2.623, 5.814)
Lung cancer	2.073 (1.266, 3.394)	1.709 (1.323, 2.208)	1.586 (1.267, 1.986)
Breast cancer	3.415 (2.12, 5.5)	2.108 (1.65, 2.693)	2.035 (1.643, 2.521)
Prostate cancer	2.34 (1.494, 3.665)	1.739 (1.364, 2.218)	1.562 (1.26, 1.937)
Colorectal cancer	2.966 (1.557, 5.653)	2.358 (1.663, 3.343)	2.269 (1.677, 3.071)
Kidney cancer	6.01 (2.3, 15.706)	3.684 (2.207, 6.149)	2.886 (1.916, 4.345)
Bladder cancer	4.729 (1.925, 11.62)	2.282 (1.5, 3.473)	2.475 (1.679, 3.648)
Leukemia	6.21 (2.59, 14.889)	4.187 (2.665, 6.578)	3.024 (2.069, 4.42)
Pancreatic cancer	1.609 (0.599, 4.322)	1.246 (0.754, 2.061)	1.441 (0.916, 2.267)
Benign neoplasms (except benign neuroendocrine tumors)	4.559 (4.018, 5.172)	3.613 (3.382, 3.859)	3.186 (3.006, 3.377)

*Censored due to low patient outcome volume

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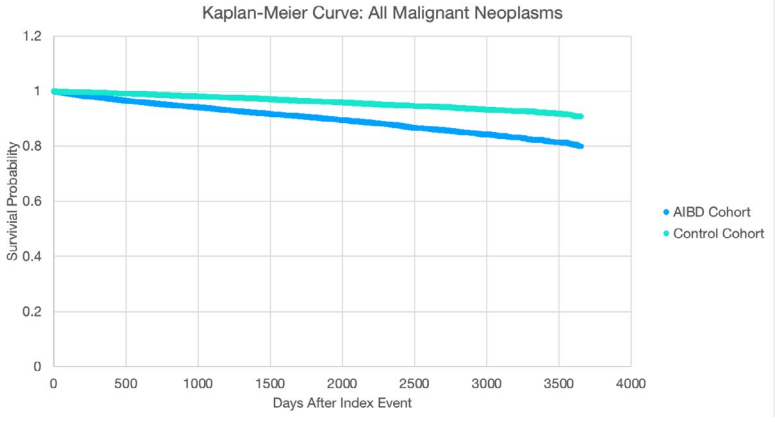
FIGURE 1. Kaplan-Meier survival curves for malignant cancer in AIBD vs controls.



Kaplan-Meier survival analysis for any malignant cancer in patients with autoimmune blistering disorders (AIBD) compared with matched controls over 10 years of follow-up. Patients with AIBD demonstrated significantly reduced survival probability, with curves diverging within the first year and remaining separated throughout the observation period.

curves, log-rank tests, and Cox proportional hazards models were used to estimate hazard ratios with 95% confidence intervals, with non-overlapping confidence intervals considered significant.

At 1 year follow-up, patients with AIBD had a significantly higher incidence of any neoplasm (including benign tumors; RD 5.95%, HR 5.61, CI 5.09-6.17) and, more importantly, any malignant cancer (RD 1.47%, HR 4.48, 95% CI 3.77-5.32) compared with controls. Elevated risks persisted at 5 (RD 9.59%, HR 3.60, 95% CI 3.42-3.78) and 10 years (RD 9.57%, HR 3.28, 95% CI 3.13-3.43). Site-specific analyses at 1 year also showed especially high risks for cutaneous cancers, including melanoma (RD 0.064%, HR 11.78, 95% CI 3.59-38.69), squamous cell carcinoma (RD 0.33%, HR 16.73, 95% CI 8.16-34.3), and basal cell carcinoma (RD 0.39%, HR 12.96, 95% CI 7.17-23.43), as well as hematologic cancers such as lymphoma (RD 0.15%, HR 15.85, 95% CI 5.74-43.8) and non-Hodgkin lymphoma (RD 0.14%, HR 19.90, CI 6.21-63.8) at one year. Risks at 1 year were modestly increased for kidney, bladder, colorectal, breast, and prostate cancers, while pancreatic cancer was not significantly associated. Results at 5 and 10 years preserved the directionality of findings (Table 1). Across malignancy types, HR was highest at 1 year follow-up and attenuated over time, but significantly elevated at 5- and 10-year follow-up, demonstrating persistently elevated malignancy risk in patients with AIBD (Table 1). Survival was lower among patients with AIBD compared to matched controls (Figure 1).

Subtype analyses revealed that pemphigoid was the major driver of malignancy risk, with consistently elevated hazards across cutaneous and hematologic cancers.[3] Pemphigus and other bullous disorders also demonstrated increased risks, particularly for skin cancers, though estimates were less precise given smaller sample sizes.

Taken together, these findings show that adults with AIBD face a persistently elevated risk of malignancies for up to a decade after diagnosis. The strongest associations were observed for cutaneous and hematologic cancers, and pemphigoid contributed most prominently to the signal. These results reinforce prior single-center observations and underscore the importance of cancer surveillance in AIBD, particularly vigilant screening for skin cancers and hematologic malignancies.[1,2,3] Limitations of this study include reliance on ICD coding, absence of treatment-level data, and potential residual confounding. Nonetheless, the large-matched cohort and long-term follow-up strengthen the validity of these findings.

DISCLOSURES

The authors have no conflicts of interest to disclose.

Ethics Statement: This study was exempt from informed consent as it involved the secondary analysis of aggregate de-identified data and does not involve interaction with human subjects. All data were de-identified in accordance with the HIPAA Privacy Rule (Section §164.514(a)), with the process attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1). This formal determination was refreshed in December 2020.

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JOURNAL OF DRUGS IN DERMATOLOGY
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INHALED, APPLIED, PRESCRIBED:
Steroids Through the Allergy Lens

HOST
Dr. Adam Friedman, MD, FAAD

GUEST
Dr. Bob Geng

We all reach for corticosteroids—whether it's that trusty tube, inhaler, or systemic burst (or maybe all of the above)—but when does "fast and familiar" become too fast for our patients' good? In this episode of the JDD Podcast Corticosteroid Stewardship Consortium Series, JDD podcast host Dr. Adam Friedman patches up with Dr. Bob Geng, Associate Voluntary Clinical Professor at UC San Diego and triple board-certified expert in allergy/immunology, clinical pharmacology, and internal medicine, to challenge some of our most comfortable prescribing habits. Auscultate to hear Dr. Geng bring a refreshingly practical, evidence tempered, and occasionally irreverent lens to steroid use, from where they still shine (and should) to the blind spots that too often slip under our radar. Together they unpack real world adverse events, the myth of "benign steroid exposure," and what true stewardship looks like across disciplines, not as a slogan, but in busy clinics where time is short and patients are counting on us. If you prescribe steroids (and let's be honest…ya do), this episode may just make you rethink your next refill. Tune in for insight, multidisciplinary perspective, and yes, a dose of good old fashioned Friedman flair.

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FEATURED CONTENT
Journal of Drugs in Dermatology

NEWS, VIEWS, AND REVIEWS

Treatment or Trigger? The Use of Biologic Therapy for Alopecia Areata

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INTRODUCTION

Alopecia areata (AA) is a chronic autoimmune disorder resulting in patchy, non-scarring hair loss on the face, body, and/or scalp.[1] It is postulated to result from the collapse of hair follicle immune privilege, which, under normal conditions, is maintained by suppressing MHC class I expression and producing immunosuppressive factors.[2] In AA, loss of this immune privilege leads to upregulation of MHC class I and II molecules, infiltration of immune cells, and the release of Th1-mediated pro-inflammatory cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF), interleukin (IL)-12, IL-15, and IL-18. This process disrupts the normal hair cycle by inducing premature catagen or telogen and ultimately resulting in hair loss.[2] The driving role of Th2-mediated cytokines in AA has also been suggested, as studies have reported elevated serum levels of IL-4, IL-13, and CC chemokine ligand (CCL)17 in patients with AA.[3] AA has also been associated with other autoimmune diseases, such as asthma, atopic dermatitis (AD), psoriasis, systemic lupus erythematosus, thyroiditis, vitiligo, and allergic rhinitis.[4-6]

Common AA treatments include topical, intralesional, or oral corticosteroids, minoxidil, cyclosporine, methotrexate, diphenylcyclopropenone, light-based therapies, and small-molecule drugs such as Janus kinase (JAK) inhibitors.[2,4] Recent case reports and case series have proposed off-label biologic therapies, such as dupilumab and secukinumab, as novel treatments for AA.[1,5,7-10] Conversely, multiple studies have reported the development of AA in patients treated with dupilumab and secukinumab.[6,8,11-15] Given this mixed evidence, this review evaluates the current literature on dupilumab and secukinumab as treatments and triggers of AA.

Biologics as Treatment

Emerging literature has reported dupilumab, an IL-4 and IL-13 receptor antagonist, as an AA treatment.[7] Currently approved in pediatric and adult patients for moderate to severe atopic dermatitis (AD), dupilumab has a well-established safety profile, with conventional adult dosing of 300 mg injected subcutaneously biweekly.[16] Dupilumab has gained increasing attention as an off-label AA treatment, particularly in patients with comorbid AD, given the potential overlapping Th2-mediated mechanisms.[5] Dupilumab may be especially useful in AA patients with elevated serum IgE, a potentially predictive biomarker for treatment response.[5] Evidence has also demonstrated reductions in Th2-related markers and increases in hair keratins in AA patients treated with dupilumab.[5]

A retrospective study of nine patients with AA and concurrent AD demonstrated significant improvement in AA on dupilumab therapy at conventional dosing, with 89% achieving a 50% improvement in their Severity of Alopecia Tool (SALT) score after 24 months.[5] Further studies have demonstrated the utility of dupilumab, with one report of complete hair regrowth after 17 months of treatment in an alopecia totalis patient refractory to typical therapies, and a case series demonstrating that seven out of ten AA patients achieved ≥50% hair regrowth after a median of eight months of treatment with conventionally dosed dupilumab.[1,7] Additionally, a recent systematic review reported that 77.5% of AA patients (n=89) experienced hair regrowth with dupilumab.[8] Overall, there is substantial evidence of successful, well-tolerated AA treatment with dupilumab, particularly in patients with comorbid AD, and additional evidence of efficacy even in patients without AD. However, the studies are largely limited to case reports, reviews with small sample sizes, and retrospective designs. Further research is needed to clarify the mechanistic details of dupilumab in AA treatment and to assess its utility in AA without concurrent AD.

Secukinumab, an IL-17 antagonist, is another biologic therapy proposed as an off-label treatment for AA. Approved for psoriasis, psoriatic arthritis, and hidradenitis suppurativa, secukinumab has also been used for AA, with one report demonstrating significant hair regrowth in a patient with a 25-year history of alopecia universalis and a 2-year history of psoriasis, three months after initiating secukinumab 300 mg monthly.[9,17] The patient subsequently experienced alopecia recurrence after discontinuing therapy six months later.[9]

IL-17 inhibition in AA management remains poorly understood. While AA is predominantly driven by Th1-mediated processes, elevated serum and lesional scalp levels of IL-17 have been reported, prompting the hypothesis for IL-17 inhibition in alopecia management.[10] However, evidence remains inconsistent and has not been clearly linked to disease severity or duration.[10] Nonetheless, the presence of elevated serum IL-17 in a subset of patients, coupled with reports of successful treatment, supports continued exploration of secukinumab in individuals with AA.

While further studies are warranted, both dupilumab and secukinumab have emerged as potential treatment options for AA in patients with comorbid conditions for which these biologics are indicated. This supports the possibility that reducing systemic inflammation from the underlying disease may also benefit AA, especially in individuals refractory to conventional treatment.

Biologics as Trigger

Although several studies have suggested dupilumab and secukinumab as potential treatments for AA, there is also growing evidence demonstrating opposing findings. A recent retrospective

study evaluating 23,782 individuals treated with dupilumab for AD found a statistically significant increase in the risk of AA after 16 weeks of conventional-dose therapy (P=0.0167).[11] Additionally, a systematic review of 89 patients on dupilumab reported new-onset or worsening AA in 22.5% of individuals, with a mean of 4.7 months after starting dupilumab; these cases resolved with treatment discontinuation, topical/intralesional/oral corticosteroids, cyclosporine, and topical minoxidil.[8] Interestingly, two patients who developed AA experienced hair regrowth after extending the dupilumab dosing interval from every two weeks to every four weeks, further highlighting the drug's potential influence on AA.[8]

While Th2 pathway suppression has been proposed to treat AA, it remains possible that Th2 suppression may lead to immune rebalancing, thereby upregulating Th1/Th17 pathways.[11] Other explanations include the unmasking of latent AA in predisposed individuals or a reflection of the inherently higher prevalence of AA among patients with AD, independent of dupilumab treatment.[11] Although evidence does not demonstrate a causal link, the prevalence of AA development during dupilumab therapy, and notably its resolution upon drug discontinuation, warrants further study.

Similarly, cases of AA developing during secukinumab treatment have been presented. A 64-year-old woman with no history of AA developed biopsy-confirmed AA 6 weeks after initiating secukinumab 300 mg monthly, with near-complete hair regrowth after discontinuation and transition to guselkumab, suggesting a secukinumab-related trigger.[12] Another report described a patient with palmoplantar pustulosis who developed rapid-onset AA within 1 week of starting secukinumab 300 mg, which progressed over several weeks and improved after discontinuation and initiation of tofacitinib.[13] Additional cases have described AA onset approximately 2–6 months after secukinumab initiation, including patients with prior adalimumab exposure, which has been associated with paradoxical AA development, or a personal/family history of AA, raising the possibility that immune priming or underlying susceptibility may contribute to this reaction.[13,14,15]

It has been suggested that secukinumab may alter the Th17 axis and upregulate Th1 pathways, leading to inflammatory destruction of hair follicles.[6] Across reports, continuation of secukinumab was generally associated with persistent or worsening alopecia despite adjunctive therapies such as intralesional corticosteroids, whereas discontinuation more consistently led to hair regrowth.[6,12,13,15] Collectively, these findings support an association between secukinumab and AA and suggest that prior biologic use, history of AA, and drug-induced immune shifts may contribute to disease development. However, it is important to note key limitations that preclude the conclusion that secukinumab is a direct trigger of AA. Many reports included patients with a prior history of AA, suggesting that cases observed during secukinumab therapy may reflect unmasking of preexisting disease rather than a direct drug effect. Prior adalimumab use may represent another area for exploring its potential influence on AA. Additionally, individuals with psoriasis have a 2.4-fold increased risk of developing AA, which may further explain its occurrence during treatment.[6] Larger prospective studies are needed to better clarify the relationship between secukinumab and AA.

CONCLUSION

This review evaluates dupilumab and secukinumab as both treatments and triggers for AA. Overall, the evidence suggests dupilumab's therapeutic potential in select patients, particularly those with comorbid AD, with stronger evidence supporting the benefit in AA treatment over triggering. Reports of AA following dupilumab initiation may reflect underlying susceptibility, including prior AA or increased baseline risk within AD populations, rather than direct causation. In contrast, secukinumab appears more frequently associated with triggering AA rather than treating. However, its exact role remains unclear due to the limited evidence and occurrences in those with pre-existing risk factors, such as prior AA, adalimumab use, and comorbid psoriasis, further complicating the association.

Overall, these findings highlight the importance of careful patient selection and close monitoring when initiating biologic therapy in individuals at risk for AA. Future prospective, controlled studies are needed to clarify the association, identify predictive biomarkers of response and risk, and better define which patient populations may benefit from or be adversely affected by biologic therapies.

DISCLOSURES

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