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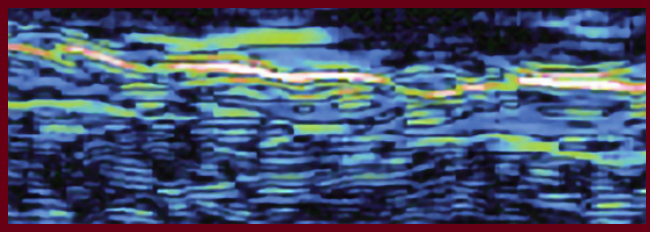


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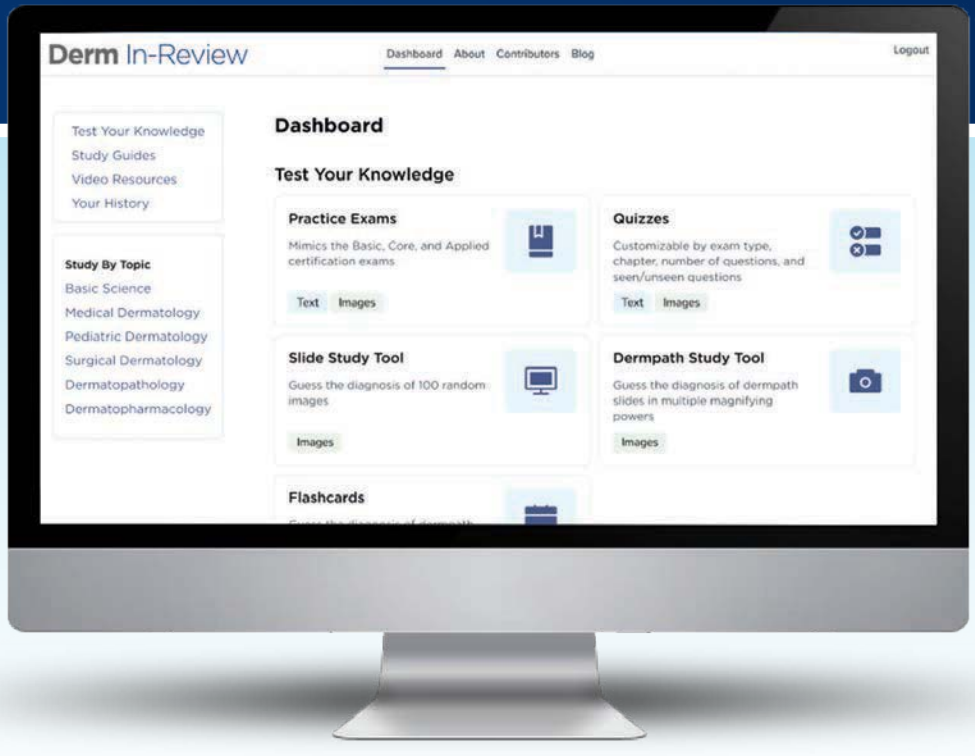
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doi:10.36849/JDD.9292

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy, Safety, and Real-World Aspects of Janus Kinase Inhibitors to Treat Patients With Alopecia Areata

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ABSTRACT

Alopecia areata (AA) is an autoimmune disease characterized by nonscarring hair loss on the scalp and body, leading to a reduced quality of life and psychosocial burden for patients. The only US Food and Drug Administration–approved treatments for severe AA are the Janus kinase inhibitors (JAKis) baricitinib, ritlecitinib, and deuruxolitinib. Herein, we discuss the efficacy, safety, and real-world aspects of JAKi treatment for patients with AA for an advanced practice provider audience. We review the clinical characteristics and diagnosis of AA and discuss treatment expectations for patients using JAKis.

J Drugs Dermatol. 2026;25(3):204-210. doi:10.36849/JDD.9292

INTRODUCTION

Alopecia areata (AA) is an autoimmune disease characterized by nonscarring hair loss on the scalp and body, with periods of relapse and remission, or complete hair loss on the scalp (alopecia areata totalis [AT]) or whole body, including the eyebrows and eyelashes (alopecia areata universalis [AU]).[1,2] Adults with AA seek outpatient primary and dermatological care more frequently than adults without AA, for both AA and comorbid conditions, negatively impacting mental health, social interactions, and employment.[3] A model predicting demands for dermatological care in the US through the year 2030 suggests that nurse practitioners (NPs) and physician assistants (PAs) will become crucial providers in the dermatology workforce to avoid shortages in care; thus, continuing to educate NPs and PAs in dermatological conditions and treatments is critical.[4]

Alopecia areata affects 2% of the global population.[1] Prevalence is higher in females than in males, which may be influenced by a greater tendency for females to seek medical care.[5] Reported incidence is greatest in Black and Hispanic/Latino patients.[6] While AA can develop at any time, the average age of diagnosis is 38.9 to 40.6 years; in a subgroup analysis, incidence is highest in adults 18 to 44 and children and adolescents 12 to 17 years of age.[5] Occurrences of AA in identical twins and siblings support that AA is hereditary;[7] genes associated with AA are involved in immune functions and Janus kinase (JAK) signaling pathways.[7] Environmental factors, including traumatic events and acute stress, also influence the development and progression of AA.[8] Pathologically, AA develops due to the loss of protection of hair follicles from immune cells (collapse in immune privilege), leading to the release of proinflammatory cytokines that activate JAK signaling pathways (Figure 1A).[9,10]

Comorbid Conditions and Psychosocial Burden

Based on a meta-analysis (n = 102 studies), autoimmune and inflammatory disorders are common comorbidities in patients with AA, including thyroid (autoimmune thyroiditis [prevalence, 41.4%] and autoimmune hypothyroidism [4.5%]), atopic (allergic rhinitis [26.5%] and allergic conjunctivitis [21.4%]), dermatological (skin infection [13.2%] and acne vulgaris [12.8%]), and rheumatic (rheumatoid arthritis [1.0%] and systemic lupus erythematous [0.3%]) diseases.[11] Additional comorbidities include cardiovascular disease (13.4%), iron deficiency anemia (6.3%), and vitamin D deficiency (1.0%).[11] A systematic review of 4 studies indicated that, globally, 66% to 74% of patients with AA suffer from psychiatric disorders, including anxiety and depression; an additional study reported that over half suffer from impaired quality of life (QoL).[12]

Clinical Presentation and Diagnosis

Alopecia areata presents as patchy hair loss without scarring or inflammation; besides minor itching and tingling, most patients are asymptomatic prior to and during AA episodes.[1,2] Hair loss may visually differ between patients depending on the AA subtype, including patchy alopecia, ophiasis, AT, and AU.[2]

Alopecia areata is typically diagnosed through clinical examination and trichoscopy, although skin biopsy might be necessary when a diagnosis is uncertain.[2,8] Clinical features of AA by trichoscopy include yellow dots, short vellus hairs, black dots, tapered hairs, broken hairs, exclamation mark hairs, upright regrown hairs, and pigtail hairs.[2] As AA is hereditary and often comorbid with other conditions, family history and medical background should be considered when diagnosing AA.[7,8,11]

Defining Alopecia Areata Disease Severity

Alopecia areata severity is evaluated by different tools in clinical trials and clinical practice. In clinical trials, AA severity and treatment efficacy are assessed using the Severity of Alopecia Tool (SALT), from which an overall AA severity score is calculated (0 [no hair loss] – 100 [100% hair loss]).[13] The Investigator's Global Assessment defines clinically meaningful scalp hair regrowth as a SALT score ≤20 (≤20% scalp hair loss).[14] Clinician-reported outcome measures assess degrees of eyebrow and eyelash hair loss and nail involvement.[15] The amount of eyebrow and eyelash hair, nail damage, QoL, and psychological symptoms are also assessed using patient-reported outcome (PRO) questionnaires.[15-17]

A different AA disease severity scale, the Alopecia Areata Scale, was developed by dermatologists in 2022 for use in clinical practice.[18] With this tool, the extent of scalp hair loss at the time of the assessment is the primary basis for determining disease severity (≤20% scalp hair loss = mild AA, 21% - 49% scalp hair loss = moderate AA, and ≥50% scalp hair loss = severe AA).[18] If AA severity is mild or moderate, a clinician can increase the AA severity rating by one level if ≥1 of the following are present: noticeable involvement of the eyebrows or eyelashes, inadequate response after ≥6 months of treatment, diffuse (multifocal) positive hair pull test consistent with rapidly progressive AA, or negative impact on psychosocial functioning resulting from AA.[18]

Treatment Options for Alopecia Areata

Treatments for AA include topical therapies (corticosteroids, calcineurin inhibitors, minoxidil, immunotherapies [dinitrochlorobenzene, squaric acid dibutylester]), intralesional corticosteroids, nonprescription therapies (aromatherapy, acupuncture), and systemic therapies (corticosteroids, oral minoxidil, dupilumab).[19] Treatment decisions depend on patient age, disease duration, and disease severity.[19] These treatments may be sufficient to treat mild or moderate AA;[19] however, in the US, the JAK inhibitors (JAKis) baricitinib, ritlecitinib, and deuruxolitinib are the only US Food and Drug Administration (FDA)-approved treatments for patients with severe AA. Baricitinib and deuruxolitinib are indicated to treat severe AA in adults;[20,21] ritlecitinib is indicated to treat severe AA in adults and adolescents ≥12 years of age.[22] The most recent Alopecia Areata Investigational Assessment Guidelines for the US from 2004[13] and expert guidance from an international group on treatment options for AA that mentions JAKis both predate the first approval of JAKis for severe AA in the US in 2022.[19,20] Thus, updated guidelines on the use of JAKis for severe AA in the US are needed. This review discusses the efficacy, safety, and real-world aspects of using JAKis for the management of patients with severe AA by NPs and PAs.

Mechanisms of Action of JAK Inhibitors in Alopecia Areata

Baricitinib and deuruxolitinib have similar mechanisms of action (MOAs) and are both oral, reversible, selective JAK1 and JAK2 inhibitors;[23,24] ritlecitinib has a distinct MOA and is an oral selective inhibitor of JAK3 and 5 members of the tyrosine kinase expressed in the hepatocellular carcinoma (TEC) kinase family (Figure 1B).[25]

Clinical Trials, Efficacy, and Safety of JAK Inhibitors for the Treatment of Severe Alopecia Areata

Baricitinib

The efficacy and safety of baricitinib was demonstrated in the double-blind, parallel-group, randomized, placebo-controlled BRAVE-AA1 (NCT03570749; Phase 2/3) and BRAVE-AA2 (NCT03899259; Phase 3) studies of adult patients with severe AA who received 2 mg or 4 mg of once-daily (QD) oral baricitinib (approved doses for severe AA) or placebo for 36 weeks (additional trial details in Figure 2).[20,23] In both trials, a significantly greater percentage of patients treated with baricitinib vs placebo achieved a SALT score ≤20 at week 36 (P<0.001 for baricitinib 2 mg and 4 mg vs placebo; Figure 3).[23]

Patients treated with baricitinib vs placebo also experienced significantly greater improvements in the Scalp Hair Assessment PRO (BRAVE-AA1: 2 mg, P=0.001; 4 mg, P<0.001; BRAVE-AA2: 2 mg, P=0.002; 4 mg, P<0.001) and eyelash and eyebrow hair regrowth (P<0.001), and a greater percentage achieved a SALT score ≤10 at week 36 (2 mg, P=0.002; 4 mg, P<0.001).[23] Response rates for both baricitinib doses increased from baseline through week 52 of treatment, and patients who achieved a SALT score ≤20 maintained this response long-term, through week 104.[26,27] Additionally, a greater percentage of patients using baricitinib vs placebo experienced improvements in health-related QoL (HRQoL), anxiety, and depression after 36 and 52 weeks of treatment.[16,17]

Over 6 months of treatment, baricitinib outperformed traditional AA treatments (topical immunomodulators, corticosteroid injections, and immunosuppressants), with a greater percentage of patients achieving SALT scores ≤20 and ≤10.[28] At week 36, the frequency and severity of adverse events (AEs) were similar between baricitinib 2-mg, baricitinib 4-mg, and placebo treatment arms, and most AEs were mild or moderate in severity (Figure 4).[23,26,27]

Ritlecitinib

The double-blind, randomized, multicenter, Phase 2b/3 ALLEGRO (NCT03732807) trial demonstrated the efficacy and safety of ritlecitinib in patients ≥12 years of age (approved dose for the treatment of severe AA is 50 mg QD; additional trial details in Figure 2).[22,25] A significantly greater percentage of patients treated with ritlecitinib 50 mg vs placebo achieved a SALT score

FIGURE 1. (A) Molecular pathology of alopecia areata and (B) mechanisms of action of JAK inhibitors. (A) In alopecia areata, the hair follicle is exposed to increased expression of major histocompatibility complex I and II and NKG2D (not shown), which leads to recruitment of CD8+NKG2D+ T cells. These T cells produce inflammatory cytokines including IFNγ and IL-15, which use JAKs for intracellular signaling. (B) Baricitinib, ritlecitinib, and deuruxolitinib inhibit JAKs to block the production of cytokines and downstream pathways in alopecia areata.

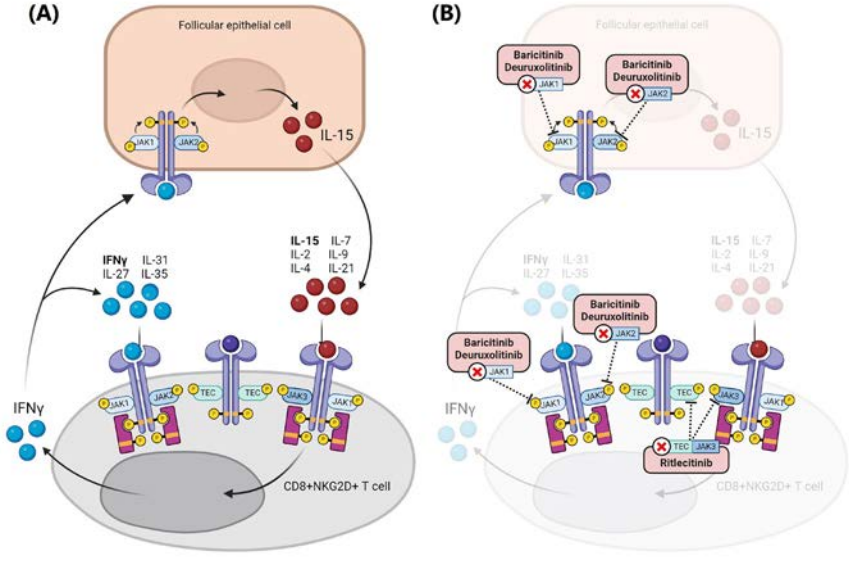


Figure created with BioRender.com.
CD, cluster of differentiation; IFNγ, interferon gamma; IL, interleukin; JAK, Janus kinase; NKG2D, natural killer group 2D; P, phosphorylation; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

FIGURE 2. Study design details from key clinical trials of baricitinib, ritlecitinib, and deuruxolitinib for the treatment of severe alopecia areata.

	Baricitinib	Ritlecitinib	Deuruxolitinib
Phase 2/3 trial name and date[a]	BRAVE-AA1 (Sep 2018–Feb 2021) and BRAVE-AA2 (Jul 2019–Jan 2021)	ALLEGRO Phase 2b/3 (Dec 2018–Dec 2020)	THRIVE-AA1 (Nov 2020–Apr 2022) and THRIVE-AA2 (Jun 2021–Jun 2022)
Trial length, weeks	36; extension through 52 and 104; ongoing	24; extension for 24; ongoing, long-term, open-label efficacy and safety study	24; open-label extension for 108; ongoing, long-term, open-label efficacy and safety study
Patient age, years	Male, 18–60; female, 18–70	Adolescents, 12–17; adults, ≥18	18–65
Inclusion criteria	SALT score ≥50 Current AA episode lasting >6 months and <8 years without spontaneous improvement	SALT score ≥50 Current AA episode ≤10 years with no terminal hair regrowth within 6 moths of screening and baseline visits	SALT score ≥50 Current AA episode lasting 6 months to 10 years
Exclusion criteria	• "Diffuse" pattern AA or other forms of alopecia • Treatment with certain topical or systemic AA therapies • Inadequate response to oral JAKis after ≥12 weeks of treatment	• Other causes of alopecia • Clinically significant depression • Auditory conditions • History of disseminated herpes simplex/zoster or recurrent herpes zoster, or adolescent patients without documented varicella-zoster virus vaccination	• History of hormonally driven AA • Recent treatment with medications that could impact hair regrowth or immune response
Primary efficacy endpoint	Percentage of patients with a SALT score ≤20 at Week 36	Percentage of patients with a SALT score ≤20 at Week 24	Percentage of patients with a SALT score ≤20 at Week 24
Key secondary efficacy endpoints	• Percentage of patients with a SALT score ≤10 at Week 36 • Percentage of patients with a Scalp Hair Assessment PRO score of 0 or 1 with a ≥2-point decrease from baseline score at Week 36 • Percentage of patients with ClinRO Measure for Eyebrow and Eyelash Hair Loss score of 0 or 1 with a ≥2-point decrease from baseline score at Week 36	• Percentage of patients with a SALT score ≤10 at Week 24 • Percentage of patients with PGI-C of moderately or greatly improved at Week 24 • Percentage of patients achieving eyebrow and eyelash regrowth through Week 48	• Percentage of patients with a SALT score ≤10 at Week 24 • Percentage of patients who responded "very satisfied" or "satisfied" on the SPRO question at Week 24 • Percentage of patients with a SALT score ≤20 at Weeks 8, 12, 16, and 20
Safety assessments	AEs Clinical laboratory tests Vital signs TEAEs	AEs Audiological testing Neurological events reviewed	AEs Clinical laboratory tests Physical examinations Concomitant medications

[a]Date ranges indicate the study start dates and primary completion dates.
AA, alopecia areata; AE, adverse event; ClinRO, clinician-reported outcome; JAKi, Janus kinase inhibitor; PGI-C, Patient Global Impression of Change; PRO, patient-reported outcome; SALT, Severity of Alopecia Tool; SPRO, satisfaction of hair patient-reported outcome; TEAE, treatment-emergent adverse event.

≤20 at week 24 (*P*<0.0001 for 200-mg loading dose plus 50-mg maintenance dose [200 to 50 mg] and ritlecitinib 50 mg vs placebo; Figure 3), with response rates increasing through week 48.[25] Additionally, significantly greater percentages of patients treated with ritlecitinib 50 mg vs placebo achieved a SALT score ≤10 (200 to 50 mg, *P*<0.0001; 50 mg, *P*=0.0003); obtained a response of moderately or greatly improved from baseline in the Patient Global Impression of Change (*P*<0.0001) at week 24, with improvements through week 48; and experienced eyelash and eyebrow regrowth over 48 weeks of treatment.[25] Ritlecitinib had similar efficacy in adult vs adolescent patients and in patients with AT vs AU.[25] With up to 24 months of treatment, 45.5% of patients achieved a SALT score ≤20.[29] Through week 24, the frequency and severity of AEs and serious AEs were similar across treatment groups; most AEs were mild or moderate in severity (Figure 4).[30]

Deuruxolitinib

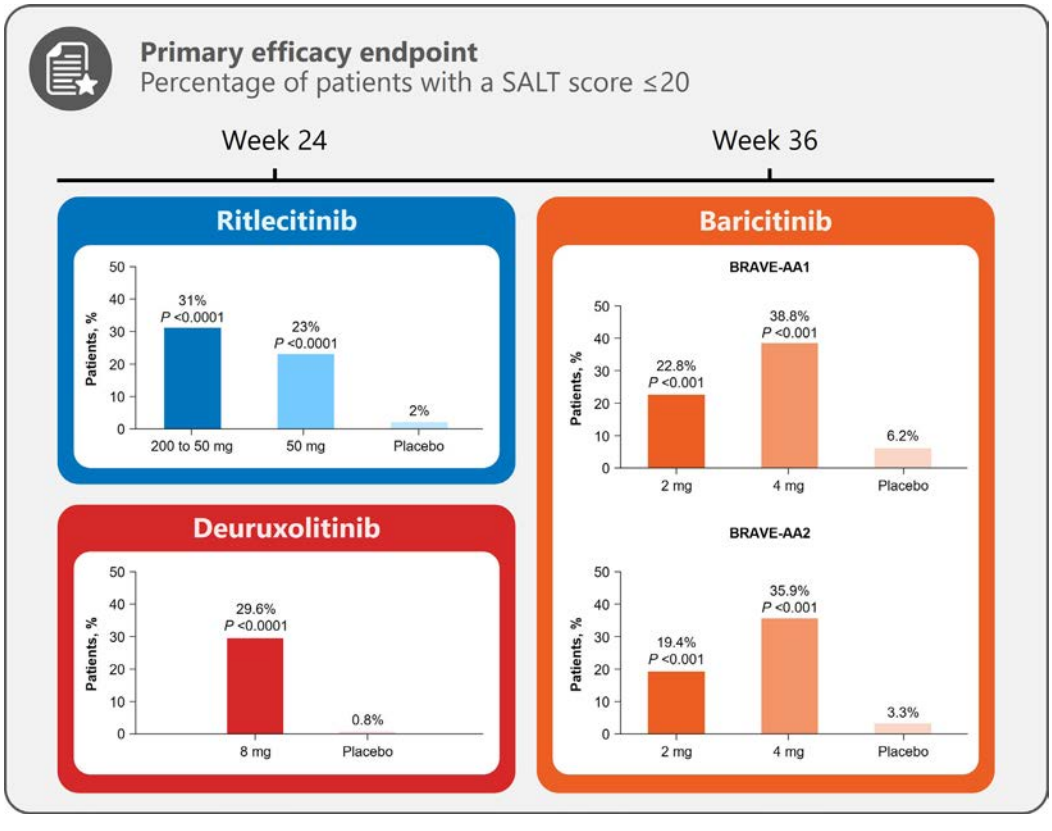
Deuruxolitinib efficacy and safety were evaluated in the double-blind, randomized, placebo-controlled THRIVE-AA1 (NCT04518995)[24] and THRIVE-AA2 (NCT04797650; submitted) studies of patients with severe AA who received 8 mg or 12 mg of twice-daily (BID) oral deuruxolitinib or placebo for 24 weeks (additional trial details in Figure 2). Deuruxolitinib 8 mg BID is approved for the treatment of adults with severe AA; deuruxolitinib 12 mg BID is not approved by the FDA.[21]

A significantly greater percentage of patients treated with deuruxolitinib 8 mg vs placebo achieved a SALT score ≤20 at week 24 (*P*<0.0001; Figure 3); a SALT score ≤20 at weeks 8 (*P*≤0.001), 12, 16, and 20 (*P*≤0.0001); and a SALT score ≤10 at week 24 (*P*≤0.0001).[24] A significantly greater percentage of patients receiving deuruxolitinib 8 mg vs placebo also reported being "very satisfied" or "satisfied" with their scalp hair in the satisfaction of hair PRO question at week 24, an improvement from baseline (*P*<0.001).[24] At week 24, the frequency and severity of AEs were similar across treatment arms, and most were mild or moderate in severity (Figure 4).[24]

Combination Therapies

In clinical settings, patients with severe AA may be treated with JAKis in combination with another AA therapy to obtain maximum therapeutic benefit (Figure 5). Though limited, evidence from smaller studies suggests combination therapies may reduce the time needed to achieve hair regrowth. In one case series, combination therapy of baricitinib 4 mg and low-dose prednisone resulted in complete hair regrowth by 3 months in 7 of 8 patients with very severe AA.[31] In a retrospective records review of 12 consecutive patients with severe AA using combined oral minoxidil with tofacitinib, 7 of 12 patients achieved a SALT score ≤20 by 9 months.[32]

FIGURE 3. Primary efficacy results from baricitinib, ritlecitinib, and deuruxolitinib clinical trials.



SALT, Severity of Alopecia Tool.

Expectations for Patients

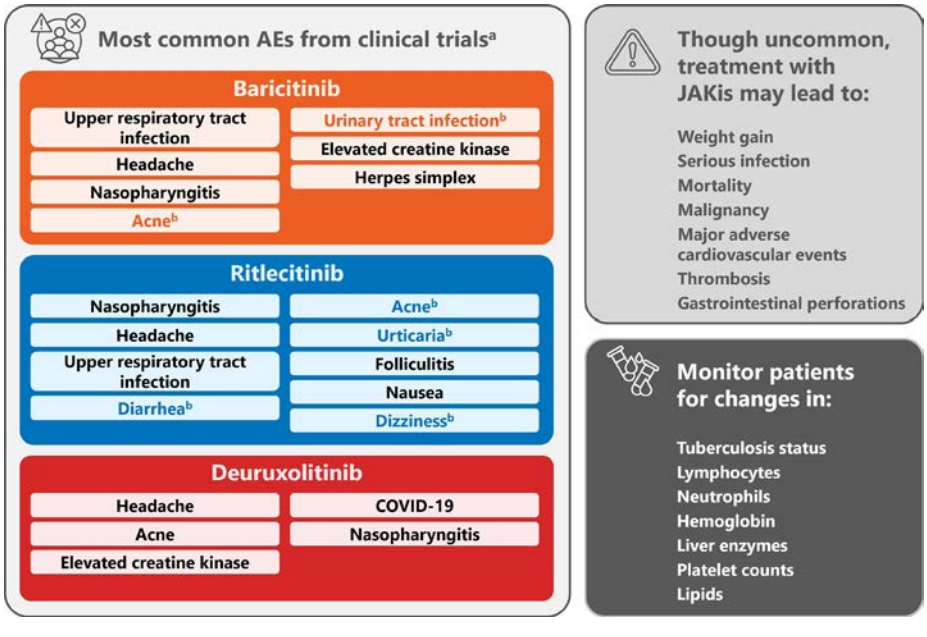
Efficacy for hair regrowth

Predictors of treatment success for patients with AA treated with JAKis include baseline disease severity and duration of current AA episode, with more severe disease and longer disease episodes associated with delayed or reduced efficacy (Figure 5).[29,33,34] Among patients receiving baricitinib up to 52 weeks, those with very severe AA had delayed and reduced response rates vs those with severe AA.[33,35] At week 24, among patients receiving ritlecitinib, those with AT or AU had lower response rates than those with partial hair loss.[25] Additionally, patients achieving a SALT score ≤20 at week 24 had less severe AA at baseline, less eyelash and eyebrow involvement, and shorter episode durations vs patients achieving a SALT score ≤20 by month 12 or 24 of treatment.[29] Similarly, for deuruxolitinib treatment, a greater percentage of patients with partial hair loss vs complete or near-complete hair loss achieved a SALT score ≤20 at week 24.[24] Notably, patients who did not achieve clinically meaningful scalp hair regrowth with baricitinib treatment still achieved eyebrow and eyelash regrowth.[17]

Impacts on HRQoL

Hair regrowth is associated with improvements in HRQoL and psychological symptoms (Figure 5). Patients with severe AA treated with ritlecitinib not only had decreased SALT scores after 24 weeks, but also experienced significant improvements in the Alopecia Areata Symptom Impact Scale.[36] Similarly, improvements in anxiety, depression, and QoL with 52-week baricitinib treatment were directly related to the amount of hair regrowth achieved.[17]

FIGURE 4. Safety considerations and monitoring of patients with alopecia areata using JAKis.



[a]AEs occurring in ≥5% of patients on approved doses of JAKis are presented from most to least common. Data from BRAVE-AA1 and BRAVE-AA2 (baricitinib), ALLEGRO (ritlecitinib), and THRIVE-AA1 (deuruxolitinib).
[b]Occurred more frequently in JAKi vs placebo treatment arms.
AE, adverse event; COVID-19, coronavirus disease 2019; JAKi, Janus kinase inhibitor.

FIGURE 5. Expectations for patients with alopecia areata treated with JAKis.



AA, alopecia areata; JAKi, Janus kinase inhibitor.

Maintenance and risk of relapse

Continuous treatment with JAKis is likely required to maintain hair regrowth, as relapse is common (Figure 5). A withdrawal period from ritlecitinib and baricitinib was associated with loss of regrown hair and worsening SALT scores, and efficacy of ritlecitinib in the 24-week retreatment period was lower than the initial 24-week treatment period.[37,38] Relapse is in part dependent on disease duration, with longer episodes associated with greater likelihood of relapse.[38] However, with continuous baricitinib treatment, approximately 90% of patients maintained clinically meaningful hair regrowth through 152 weeks.[38]

Common and Rare Side Effects and Patient Monitoring

Across baricitinib, ritlecitinib, and deuruxolitinib clinical trials, most AEs were mild or moderate in severity; the most common AEs are presented in Figure 4.[23,24,30] No changes in vital signs, except increased weight gain, were observed.[24,28] However, reduced hemoglobin, neutrophils, and lymphocytes; elevated low- and high-density lipoprotein and creatine kinase; and increased and decreased platelet counts were observed; most changes were not clinically meaningful.[23-25] Thus, laboratory tests are required before and during JAKi treatment, including latent tuberculosis tests.[20-22]

While most AEs from clinical trials were mild or moderate, serious infections, mortality, malignancy, major adverse cardiovascular events, thrombosis, and gastrointestinal perforations are potential rare side effects of JAKi treatment listed as boxed warnings.[20-22] After 36 weeks of baricitinib treatment or 24 weeks of ritlecitinib or deuruxolitinib treatment, herpes zoster infection (baricitinib: 2 mg, 4/338 patients; 4 mg, 5/513; ritlecitinib: 200 to 50 mg, 1/131 patients; 50 mg, 5/130; deuruxolitinib: 8 mg, 1/350 patients), serious infections (baricitinib: 2 mg, 2/155 patients; 4 mg, 1/233; ritlecitinib: 200 to 50 mg, 2/131 patients; deuruxolitinib: 8 mg, 1/350 patients), cardiovascular events (baricitinib: 2 mg, 1/183 patients; ritlecitinib: 50 mg, 1/130 patients), and malignancies (baricitinib: 4 mg, 1/233 patients; ritlecitinib: 200 to 50 mg, 1/131 patients; 50 mg, 1/130) occurred infrequently.[23-25] Over 104 weeks of baricitinib and 24 months of ritlecitinib treatment, most AEs remained mild or moderate in severity; only 1 case of deep vein thrombosis (baricitinib) and 1 death (ritlecitinib; unrelated to study drug) occurred over the longer treatment durations.[27,39] However, since the chronic nature of AA suggests that patients could receive long-term JAKi treatment, continued long-term efficacy and safety studies are warranted.

CONCLUSION

In summary, JAKis are effective treatments for patients with severe AA, which causes patchy hair loss and a significant psychosocial burden for patients. Depending on the disease severity and AA episode duration, patients may experience variable responses to JAKis and will likely require long-term treatment to prevent relapse, which may increase the risk of experiencing a rare but serious AE. However, data from Phase 3 studies of baricitinib, ritlecitinib, and deuruxolitinib demonstrate that treatment for 24 or 36 weeks improves not only hair regrowth but also QoL; thus, JAKis are beneficial treatments for patients with severe AA.

DISCLOSURES

DD serves as a speaker and/or is an advisory board member for AbbVie, Amgen, Arcutis Biotherapeutics, Beiersdorf, Dermavant Sciences, Galderma, Johnson & Johnson, LEO Pharma, Lilly, Novartis, Sanofi/Regeneron, Takeda, and UCB. KK serves as a speaker and/or is an advisory board member for AbbVie, Amgen, Arcutis Biotherapeutics, Beiersdorf, Bristol Myers Squibb, Castle Biosciences, Ferndale, Galderma, Janssen, Johnson & Johnson, LEO Pharma, Novartis, Pfizer, Sun Pharma, Takeda, and UCB.

ACKNOWLEDGMENT

Medical writing and editorial support were provided by Jordyn Karliner, PhD, of Red Nucleus, and funded by Sun Pharma.

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March 2026

The Importance of Quality Skincare for Barrier Repair During Acne Therapy

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JOURNAL OF DRUGS IN DERMATOLOGY
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Abstract

Acne is a common chronic inflammatory disorder with multifactorial pathophysiology. One factor, impaired barrier function, has until recently been underappreciated. Data shows that acne-prone skin displays an inherent barrier deficiency highlighted by increased transepidermal water loss and substantive abnormalities in stratum corneum proteins and lipids. Acne therapy often involves exfoliants and irritants such as hydroxy acids, benzoyl peroxide, and retinoids that can exacerbate the barrier dysfunction.

The clinician's role in acne care is to devise a treatment regimen that is tailored to the individual patient, including topical and oral medications to address the underlying pathogenesis of acne. They also play a crucial role in recommending appropriate adjunctive nonprescription therapy. Over-the-counter products aid in acne therapy in numerous ways: lesion reduction, repair of the inherent barrier dysfunction, and maintenance of stratum corneum health during prescription treatment.

Barrier repair reduces the symptoms of irritation, which often lead to nonadherent medication behavior and subsequent reduced efficacy. This review is intended to provide a primer on skin care in acne and to highlight evidence-based advances in cleansers and moisturizers that serve as cornerstones for optimized acne therapy.

Introduction

Acne is a common multifactorial inflammatory skin condition affecting up to 50 million Americans.[1] Traditional tenets of acne pathophysiology have indicated four central factors: hyper-and dysseborrhea, *Cutibacterium acnes* colonization, hyperkeratinization, and inflammation. More recently, studies have implicated the role of skin barrier dysfunction as a material contributor to the pathophysiology of acne. There is altered expression of barrier molecules, including filaggrin, involucrin, keratin, desmoglein, and aquaporin-3, proteins that regulate cohesion, desquamation, and hydration, resulting in compromised barrier integrity.[2,3] Increased transepidermal water loss (TEWL), increased pH, decreased microbial diversity, and decreased ceramide levels have been demonstrated, with the extent of the abnormality directly proportional to the severity of disease.[4,5] This leads to skin dryness, irritation, and increased sensitivity.[6]

Combined, these data suggest that the barrier function of acne-prone skin is inherently abnormal at baseline. Barrier dysfunction is accompanied by hyperkeratosis of the follicular epithelium, and Yamamoto and others have posited that this could promote comedone formation.[4,7,8]

In addition to the inherent barrier dysfunction, the use of topical medications and over-the-counter (OTC) acne products often results in side effects of skin dryness and irritation as a consequence of their keratolytic, sebostatic, and bacteriocidal activities.[7,9-15] Benzoyl peroxide has been shown to damage the barrier and disrupt the microbiome in a concentration- and vehicle-dependent manner; increased sebum levels, increased TEWL, decreased hydration, and decreased microbial diversity are the consequences of its use.[16] Topical retinoids and chemical peels also disrupt the barrier and may temporarily strip the microbiome.

Harsh cleansers are often chosen by uninformed oily acne patients due to their antimicrobial claims. They contribute to barrier dysfunction by further stripping natural moisturizing factor (NMF) compounds and lamellar lipids. Together, the net result is the exacerbation of the inherent barrier deficiency, which affects compliance with therapy.[17-22]

Acne treatment guidelines recommend that the acne management paradigm be built upon a foundation of benzoyl peroxide and a retinoid.[23] Studies and expert consensuses have concluded that the use of gentle cleansers and quality moisturizers can minimize the adverse events of dryness and irritation.[7,24,25] Adherence to acne regimens, particularly in the teenage population, is notoriously poor, and iatrogenic skin irritation is a common factor leading to that nonadherent behavior.[17,26,27] Specifically, side effects of stinging, burning, redness, and dryness were found to be major reasons for nonadherent behavior.[28-31] Adding moisturizers to medication regimens improves adherence by decreasing side effects and improving acne lesion count.[15,20,21] Feldman and Chen also noted that irritation resulted in an increase in office complaint call-backs and loss of faith in the provider.[22] Ultimately, improved adherence resulting from good skin care allows for maximum treatment outcomes.[7,13,33-35]

Baseline Stratum Corneum Deficiencies in Acne-Prone Skin

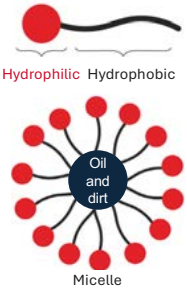
Acne is associated with a decrease in filaggrin[2] and aquaporin-3 proteins[3].These epidermal proteins are necessary to sustain stratum corneum hydration and barrier function. Filaggrin breaks down into NMF in the corneocytes[36-38] and aquaporins transport water from the viable layers of the epidermis to the stratum corneum.[3,39,40] Deficiency in either protein results in decreased water-holding capacity of the stratum corneum and overall dysfunction.[3,39,40] Stratum corneum hydration is critical for the delicate balance of enzymes responsible for desquamation.[41-44] Under low moisture circumstances, there is an accumulation of nonviable cells that may occlude the follicle leading to acne.[45,46] The overall goal of skin care is to use cleansers that do not worsen the baseline abnormalities by stripping still more filaggrin and lipids, and moisturizers that hydrate the skin and replenish the missing components.

Cleansing

It is generally understood that cleansing is an important part of skin hygiene, removing dirt, oil, microorganisms, and allergens. However, cleansing with harsh surfactants can cause more harm than good by removing essential lipids, natural moisturizing factors, and beneficial microorganisms. Particularly in acne patients, it is important not to disturb the barrier any further than baseline, as this can worsen acne and decrease the patient's ability to use beneficial medications. It is useful in this regard to consider acne-prone skin to be analogous to clinically diagnosed sensitive skin and to make choices accordingly. Surfactant choice, pH, and patient preference figure into our decisions.

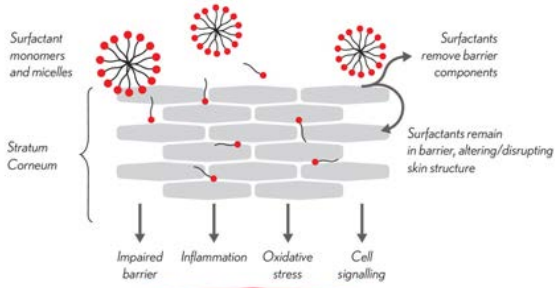
All cleansers rely on surfactants to remove dirt and oil. Surfactants are amphiphilic molecules with a hydrophilic head and hydrophobic tail (Figure 1).

Figure 1. Surfactant structure.



In water, they tend to assemble into micelles and bind impurities within, while the outward-facing hydrophilic heads allow the entire assembly to be rinsed off with water. Surfactant charge (neutral, anionic, cationic, amphoteric) and micelle formation determine both the mildness of the cleanser and its foaming action. When alkaline detergents are used, free surfactant monomers are able to penetrate the skin where they interact with proteins and lipids, causing the sensation of skin tightness and the outcome of irritation and itch (Figure 2).

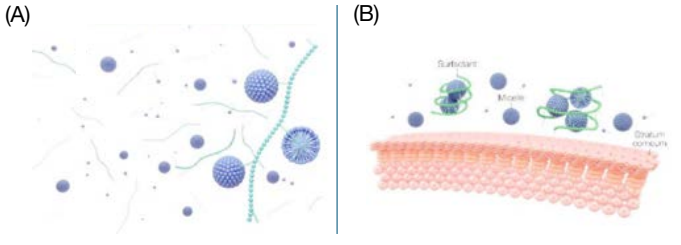
Figure 2. Damaging effects of harsh surfactants.



Adapted from Walters RM, *Derm Res Pract.* 2012.495917

Polymeric surfactant cleansing technology (PCT) is one method by which micelle penetration can be limited. It strikes a balance between effective cleansing and foaming while minimizing irritation. Hydrophobically modified polymers such as potassium acrylate copolymer interact with the hydrophobic tails of the surfactant, creating large micelles that fail to penetrate the stratum corneum; there is also a decrease in the concentration of free surfactant monomers (Figure 3A). This allows for the use of increased cleanser concentrations that promote higher quality foaming ability. The use of sodium hydrolysed potato starch dodecenylsuccinate (SHPSD) in addition to PCT or as a standalone creates even larger complexes that create rich foam without irritation (Figure 3B). Biodegradability is an additional benefit. Although rich foam is not a required component for an effective cleanser, most patients, especially oily-skin acne patients, prefer cleansers that lather well.

Figure 3. (A) Binding of micelles by hydrophobically modified polymer (B) Additional binding of potato-starch surfactant to increase micelle size.



Cleanser pH is an important characteristic to consider. The physiologic pH of the skin is acidic: between 4 and 6. Within this range, the stratum corneum functions to its highest capacity. Enzymes associated with differentiation and desquamation are optimized, the microbiome is more physiologic and there is a decrease in inflammation.[13,47] The pH of acne-prone skin is higher at baseline, making skin more prone to irritation from medications.[48] Quality cleansers with low pH can normalize the pH, thus improving barrier function and decreasing inflammation.[8,27,49,50]

A Hydrating Gel Cleanser uses PCT in combination with SHPSD, producing large micelles, less irritation, and superior foaming ability. In a study of 85 subjects with sensitive skin, including acne, use of the cleanser resulted in the absence of increased TEWL, no change in pH, and a statistically significant reduction in overall skin appearance and symptoms of stinging, itching, burning, and tightness after 2 and 4 weeks of daily use.[51] There was also no change in the microbiome, NMF levels, or lipid markers, indicating the absence of skin stripping. It is worth noting that it is unusual to see *improvements* in skin appearance, such as softness and smoothness, following the use of a cleanser – these are qualities that are normally attributed to moisturizers. It is a testament to the gentleness of the polymer cleansing technology that such a result is possible without additional products.

Another cleanser specifically intended for acne-prone skin uses the SHPSD combined with a novel salicylic acid formulation. Conventional salicylic acid has low water solubility, which limits its permeability and therefore efficacy when used topically. Additionally, when combined with foaming surfactants, salicylic acid is often drying. Overall, conventional salicylic acid cleansers can result in irritation without displaying significant efficacy against acne. A novel 2% salicylic acid cleanser uses a microgel complex that contains cetyl lactate and alkyl lactate that dissolve sebum, allowing the salicylic acid to penetrate deeper into the follicle[52] (Figure 4). The addition of SHPSD increased the aesthetically pleasing foaming capacity of the cleanser without causing irritation. In a study of 35 subjects over 12 weeks of daily use, 33.7% saw a decrease in total lesion count.[52] This was accompanied by a statistically significant improvement in overall appearance. There was no change in ceramides, cholesterol, or free fatty acid, indicating no disruption in barrier lipids.[52]

Moisturizers

Quality moisturizers that restore and maintain barrier function have numerous characteristics (Table 1). Humectants are hygroscopic molecules that attract and bind water, increasing stratum corneum hydration. Common humectants include NMFs, glycerin, and hyaluronic acid. Occlusives provide a barrier to prevent water loss and to protect the skin surface from pathogens and allergens. Petrolatum, silicones, lanolin, and mineral oil all function to seal moisture within the stratum corneum. Emollients such as cetyl and steryl alcohol, as well as plant oils, serve to smooth the skin. Physiologic lipids such as ceramides, cholesterol, and free fatty acids together in equimolar concentrations comprise the lipid bilayer (Figure 5). Topically applied, they are incorporated into the lipid bilayer, augmenting and/or replacing missing or dysfunctional ingredients in diseased skin. Cosmeceuticals (agents that are at the juncture of cosmetics and drugs) are often added to moisturizers to augment the occlusive or humectant qualities of the product, as well as adding soothing, anti-inflammatory, and antioxidant qualities.

Figure 4. Microgel complex increases salicylic acid (red) in pilosebaceous unit compared to conventional salicylic acid.

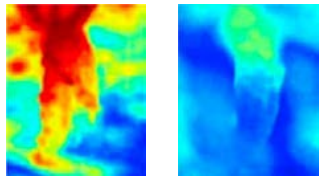
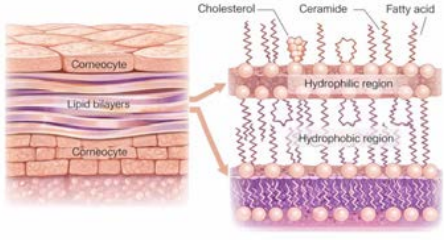


TABLE 1. Considerations for Moisturizer Ingredients for Acne-Prone Skin

	Purpose	Example Ingredients
Humectants	Attract and bind water	Glycerin, hyaluronic acid, NMFs (urea, amino acids, electrolytes, lactate, PCA)
Occlusives	Skin protective, decreased TEWL	Petrolatum, silicones, lanolin, mineral oil
Emollients	Smooth skin	Cetyl alcohol, steryl alcohol, plant oils (sunflower, safflower, avocado, coconut)
Physiologic lipids	Repair and support of lipid bilayer, decreased TEWL	Ceramides, cholesterol, free fatty acids
Cosmeceuticals	Anti-inflammatory, anti-oxidant, occlusive	Allantoin, panthenol, niacinamide, vitamin E, linoleic acid, *Centella asiatica*, probiotics

NMF: Natural moisturizing factor, PCA: Pyrrolidone carboxylic acid, TEWL: Transepidermal water loss

Figure 5. Healthy lipid bilayer structure.



Importance of the Skin Microbiome in Barrier Health

The skin barrier comprises physical, chemical, and microbial components that function together to maximize skin health. The stratum corneum and microbiome have a mutualistic relationship. The skin provides a niche in which live moisture and food. The microbiome, in turn, occupies the niche and consumes the nutrients that might otherwise be taken/consumed by pathogens, acidifies the stratum corneum, making it less hospitable to pathogens like *S. aureus*, and aids in host defense and innate immunity. Changes in either barrier composition or microbial communities impact the other. In acne, both systems are often disrupted. As mentioned previously, innate barrier dysfunction is a hallmark of acne-prone skin. The use of topical retinoids, benzoyl peroxide, hydroxy acids, and isotretinoin are all associated with barrier disruption, decreased hydration, and increased TEWL. Additionally, topical and oral antibiotics, as well as isotretinoin, alter the cutaneous microbiome. These changes may contribute to increased inflammation and iatrogenic irritation, as well

as reduced treatment adherence, resulting in decreased therapeutic efficacy. Moisturizers are necessary to enhance hydration, replenish intercellular lipids, and help to stabilize the microbiome. As such, moisturizers function as prebiotics, and postbiotics like succinic acid can also be incorporated to promote microbiome health.

Moisturizers for Acne-Prone Skin

Traditional moisturizers that are intended to reduce skin sensitivity and irritation contain large amounts of occlusives and emollients that may be counterproductive for acne-prone skin. These ingredients are often comedogenic and leave unpleasant greasy residues that acne patients find particularly unpleasant, leading to poor compliance. Acne patients often have a combination of excess sebum with acne-related and medication-related dryness and need to be reminded that sebum is not a moisturizer. What is needed for acne patients is a lightweight moisturizer that provides hydration without a greasy residue, does not clog pores, is nonirritating to sensitive acne-prone skin, and helps to combat iatrogenic irritation.

A gel-matrix moisturizer (Hydroboost® Gel Cream Moisturizer) and a water-cream moisturizer (Hydroboost® Water Cream Moisturizer) have been studied in acne patients.[53,54] Both products contain NMF components (amino acids, electrolytes, urea, PCA, lactate) as well as glycerin and hyaluronic acid as humectants to attract and bind water, dimethicone as an occlusive, and cetyl alcohol as an emollient. Additionally, the water cream contains physiologic lipids: ceramides, cholesterol, and free fatty acids. Both products are lightweight and residue-free with the water-cream having a richer texture due to the physiological lipids.

Both products were evaluated in preclinical and clinical studies.[53,54] Skin explants were used for the preclinical studies that showed, after 2-3 days, an upregulation of genes involved in synthesis, metabolism, and exportation of lipid precursors, an increase in the levels of filaggrin, aquaporin-3, hyaluronic acid, and neutral lipids. These findings indicate that the products are not just adding moisture to the skin; they are triggering epidermal repair from within. Clinically, after 4 weeks of once to twice daily use, there was a decrease in TEWL and an increase in hydration, which persisted during a 3-day regression. There was a significant improvement in all parameters of skin health, including erythema, peeling, flaking, drying, itch, tightness, and overall skin sensitivity. Patients who were concomitantly on acne medications noted an increase in compliance with their prescribed products.

Conclusion

Skin barrier repair and maintenance in acne serves two distinct purposes: repair of baseline barrier dysfunction and improved medication adherence with optimized efficacy. Due to the innate barrier dysfunction in acne-prone skin, maximizing barrier and microbiome health may alone result in acne improvement. Small studies have demonstrated that quality skincare can reduce TEWL, acidify the skin pH, and foster the growth of a healthy microbiome.[55] This may offer an explanation for the unexpectedly positive results seen in the vehicle arms of recent phase 3 acne studies; improved vehicle technology, as well as dispensing quality skin care for study subjects, may augment the efficacy of the active ingredient. Second, the use of appropriate skin care to improve pharmacologic tolerability and adherence is associated with superior clinical outcomes.

A holistic approach to all dermatologic conditions, including cleansing, moisturization, and sun protection in addition to prescription therapy is recognized as essential to skin health. Patient education regarding the importance of adjunctive therapy is crucial to ensure the use of quality products and the avoidance of potentially harmful agents touted in internet fads. However, time constraints in a busy office often means that skincare takes a back seat. Additionally, it is important to tailor product recommendations to the individual patient. Considerations include the severity of the acne, patient preference for aesthetic qualities of cleansers and moisturizers, and consequential adherence. Also important in the decision-making process is anticipating the irritation potential of the topical acne products being prescribed. Recent advances in vehicle technology have provided clinicians with superior products with improved tolerability. Unfortunately, affordability is often a deterrent to accessing such medications. Quality cleansers and moisturizers that help to restore and maintain barrier function are crucial for such patients.

A comprehensive approach to acne care must incorporate adjunctive skincare with careful attention to ingredient and formulation selection and patient preference that aid clinicians in optimizing clinical results. Given the expansive selection of commercial cleansers and moisturizers and excessive internet noise, it is important to combat patient choice paralysis by providing specific brand-name recommendations and use instructions.

Disclosure

Dr Baldwin serves as an advisor to Beiersdorf, Galderma, Kenvue, La Roche-Posay, and L'Oreal.

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doi:10.36849/JDD.9739

March 2026 211 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Brodalumab's 8-Year Journey in Plaque Psoriasis: Insights Into Efficacy, Safety, and Real-World Evidence

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ABSTRACT

Background: Plaque psoriasis is a chronic immune-mediated disease driven by proinflammatory cytokines. Brodalumab—a recombinant, human monoclonal antibody that functions as an interleukin-17 receptor A blocker—was approved in 2017 in the United States for treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic or phototherapy and have failed to respond to/have lost response to other systemic therapies. While efficacy and safety of brodalumab for moderate-to-severe plaque psoriasis were demonstrated across phase 2 and 3 clinical trials, long-term data from these trials and several real-world studies have since been published.

Methods: In this review, we summarize efficacy/safety findings from long-term clinical trials and real-world studies. Updated US pharmacovigilance data collected over 8 years of clinical brodalumab usage are also provided.

Results: Across clinical trials and real-world studies, brodalumab consistently delivered rapid skin clearance, high rates of complete response, and sustained disease control, even among patients who have not achieved adequate benefit with other biologics. An integrated analysis of 5 clinical trials showed brodalumab was well tolerated and not associated with increased risk of malignancy, major adverse cardiac events, suicidal ideation/behavior, or fatal adverse events over 52 weeks. This, combined with 8 years of pharmacovigilance experience, affirms a stable safety profile, with no new safety signals and no demonstrated causal links to increased psychiatric events.

Conclusion: These findings reinforce that brodalumab is an important, well-tolerated therapeutic option for achieving high levels of disease control in patients with moderate-to-severe psoriasis, including those with prior biologic exposure or difficult-to-treat disease manifestations.

J Drugs Dermatol. 2026;25(3):211-220. doi:10.36849/JDD.9739

INTRODUCTION

Plaque psoriasis is a chronic immune-mediated disease driven by proinflammatory cytokines, such as interleukin (IL)-17, IL-12, IL-23, and/or tumor necrosis factor-alpha (TNF-alpha).[1,2] The joint American Academy of Dermatology and National Psoriasis Foundation guidelines for the management of moderate-to-severe psoriasis include biologics, which are monoclonal antibodies and fusion proteins that block specific cytokines or cytokine receptors critical to psoriasis pathogenesis.[2] Brodalumab—a recombinant, human monoclonal antibody—was approved in 2017 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy in the European Union (Kyntheum; LEO Pharma)[3] and, in the US (Siliq® subcutaneous injection; Bausch Health Companies Inc.), for adults who are candidates for systemic or phototherapy and have failed to respond to or have lost response to other systemic therapies.[4]

A key contributor to the pathophysiology of psoriasis is IL-17.[5] Once released from immune cells, IL-17 directly activates keratinocytes, driving their proliferation and release of psoriasis-associated chemical messengers, which in turn activate more immune cells, resulting in a feedback loop that promotes further IL-17 release.[6] While other approved biologics target the IL-17

FIGURE 1. Brodalumab mechanism of action.

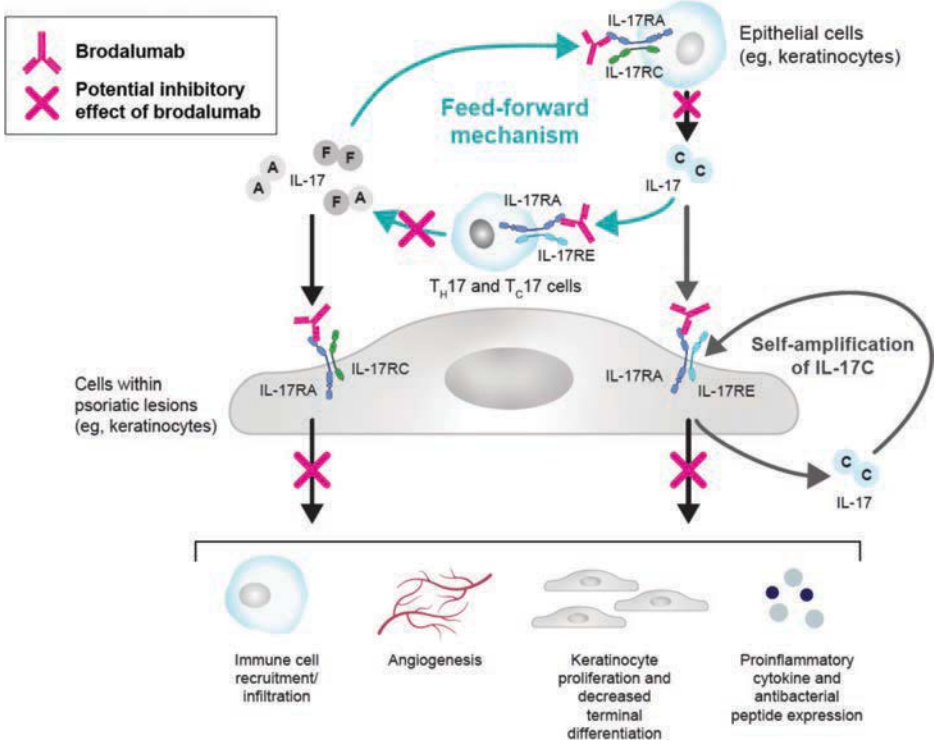


Figure adapted from Han et al.[45] and reprinted with permission from Springer Nature.
IL, interleukin.

cytokine isoforms IL-17A or IL-17A/F, brodalumab is the only approved biologic that functions as an IL-17 receptor A (IL-17RA) blocker (Figure 1),[7] which in turn inhibits the downstream signaling of multiple IL-17 isoforms including IL-17A, IL-17C, IL-17E, IL-17F, and IL-17A/F.[4] Further, brodalumab is one of only two FDA-approved biologics for the treatment of plaque psoriasis that inhibit IL-17F signaling,[8] which, along with IL-17A, is the primary cytokine in psoriasis plaques.[9] This broad inhibition of IL-17 signaling could enhance the likelihood of rapid, deep, and durable disease control.[6,10]

While the efficacy and safety of brodalumab for moderate-to-severe plaque psoriasis have been established across one phase 2 and three phase 3 clinical trials,[11-13] in the 8 years since brodalumab's approval, long-term data from these trials have been published,[14,15] and several real-world studies have also been conducted.[5,16-21] In this review, we summarize these brodalumab efficacy and safety findings along with US pharmacovigilance data collected over 8 years of clinical usage that attest to the long-term safety characteristics of brodalumab.

Efficacy

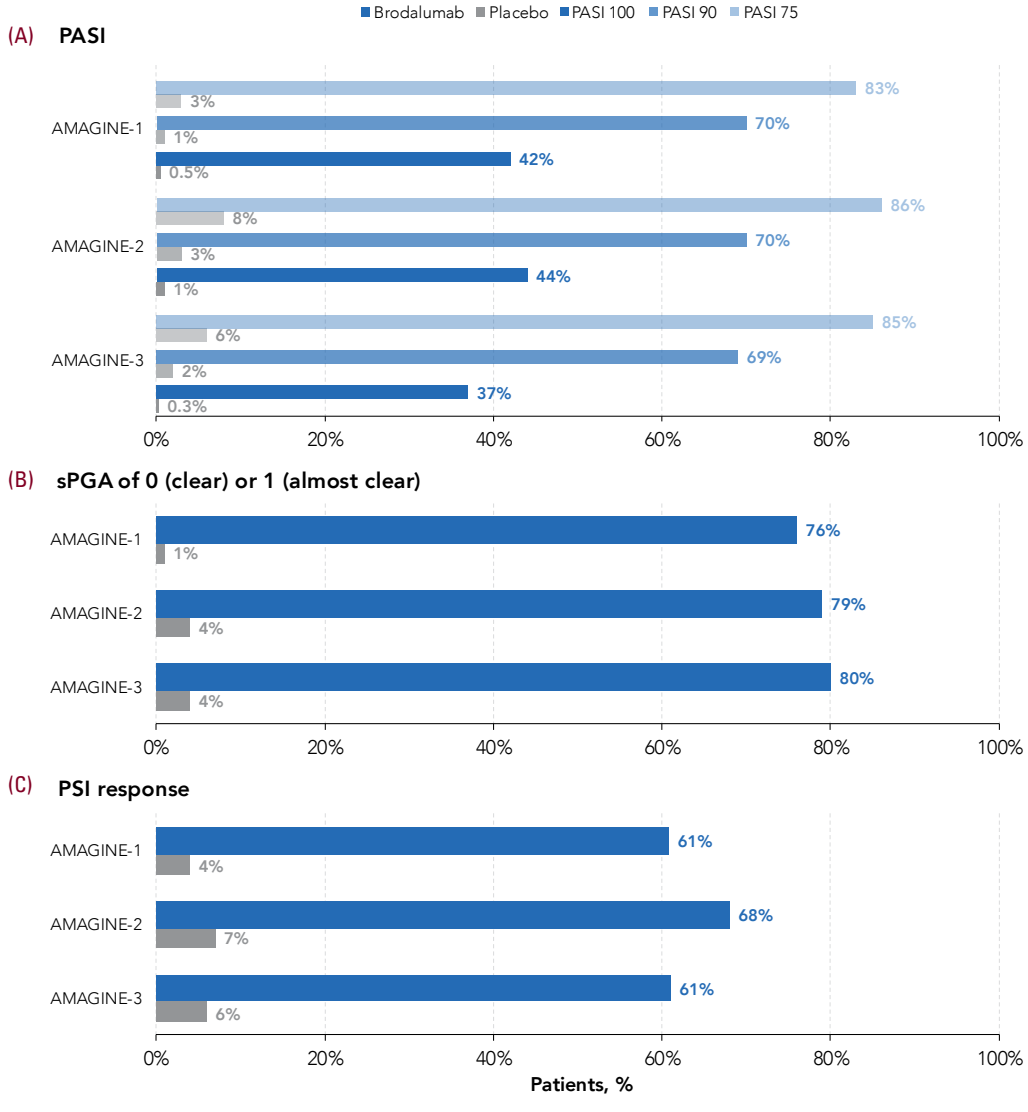
Pivotal Clinical Trials

The efficacy of brodalumab for moderate-to-severe psoriasis has been demonstrated across three pivotal phase 3 trials.[12,13] The AMAGINE-1,[12] AMAGINE-2,[13] and AMAGINE-3[13] trials included a 12-week induction phase, followed by a 40-week maintenance phase and open-label extension studies thereafter.[14,15] Patients were randomized to receive brodalumab (140 or 210 mg), placebo, or an active comparator (an IL-12/23 inhibitor, ustekinumab; AMAGINE-2 and -3 only) in the 12-week induction period. This review summarizes efficacy data for the approved brodalumab dose of 210 mg only.[4] Efficacy of brodalumab compared with ustekinumab is discussed later (see section titled *Subgroup Analysis: Efficacy in Patients With Inadequate Response to Other Biologics).*

Week 12

At week 12, skin clearance rates were significantly higher with brodalumab versus placebo, with at least a 75% reduction in the Psoriasis Area and Severity Index score (PASI 75), PASI 90, and PASI 100 (complete skin clearance) achieved by 83%–86%, 69%–70%, and 37%–44% of patients treated with 210 mg of brodalumab, respectively (Figure 2A). The median time to PASI 75 across the 3 trials was 4 weeks, and median time to PASI 90 and PASI 100 in AMAGINE-1 were 6 and 12 weeks, respectively. In patients treated with brodalumab at week 12, rates of static Physician's Global Assessment (sPGA) score of 0 or 1 (clear/almost clear skin) were 76%–80% and rates of participant-reported Psoriasis Symptom Inventory (PSI) response (total score of ≤8) were 61%–68% (Figure 2B, C).

FIGURE 2. Brodalumab efficacy across pivotal phase 3 trials at week 12.[12,13]



Brodalumab dose of 210 mg Q2W. Number of patients at week 12: brodalumab/placebo AMAGINE-1, n=222/220; AMAGINE-2, n=612/309; AMAGINE-3, n=624/305. Missing values were imputed as nonresponses. PASI 75, 90, and 100 represent the proportions of patients achieving at least 75%, 90%, and 100% reductions in PASI score from baseline. PSI response defined as a total score of up to 8, with no item having a score greater than 1 (total possible score ranges from 0 [best] to 32 [worst]). Clinical trials evaluating the efficacy and safety of brodalumab in patients with psoriatic arthritis have been conducted but are out of the scope of this review.[46]
PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, once every 2 weeks; sPGA; static Physician's Global Assessment.

TABLE 1.

Long-Term Brodalumab Efficacy Across Pivotal Phase 3 Trials

% Patients	Week 52[12,13] (non-responder imputation)			Week 120[14,15] (observed/non-responder imputation)	
	AMAGINE-1	AMAGINE-2	AMAGINE-3	AMAGINE-1	AMAGINE-2 and -3 (pooled)
PASI 75	NR	80	80	96/80	96/37
PASI 90	78	75	73	84/70	86/33
PASI 100	68	56	53	74/61	74/29
sPGA 0/1	83	63	61	86/71	NR

Brodalumab dose of 210 mg Q2W. Number of patients at week 52: AMAGINE-1, n=83; AMAGINE-2, n=334; AMAGINE-3, n=342. Number of patients at week 120 (observed/NRI): AMAGINE-1, n=69/83; AMAGINE-2, -3 (pooled), n=132/339. PASI 75, 90, and 100 represent the proportions of patients achieving at least 75%, 90%, and 100% reductions in PASI score from baseline. Psoriasis Symptom Inventory (PSI) response rates generally not reported. Observed and non-responder imputation rates reported for week 120. Non-responder imputation assumes nonresponses for all missing data. Response rates from observed data may be impacted by high numbers of missing data resulting from sponsor decision to terminate the AMAGINE trials during the long-term extension phase; similarly, it may be unfair to assume that unobserved outcomes are uniformly nonresponders. Clinical trials evaluating the efficacy and safety of brodalumab in patients with psoriatic arthritis have been conducted but are out of the scope of this review.[46]
NR, not reported; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; Q2W, once every 2 weeks; sPGA; static Physician's Global Assessment.

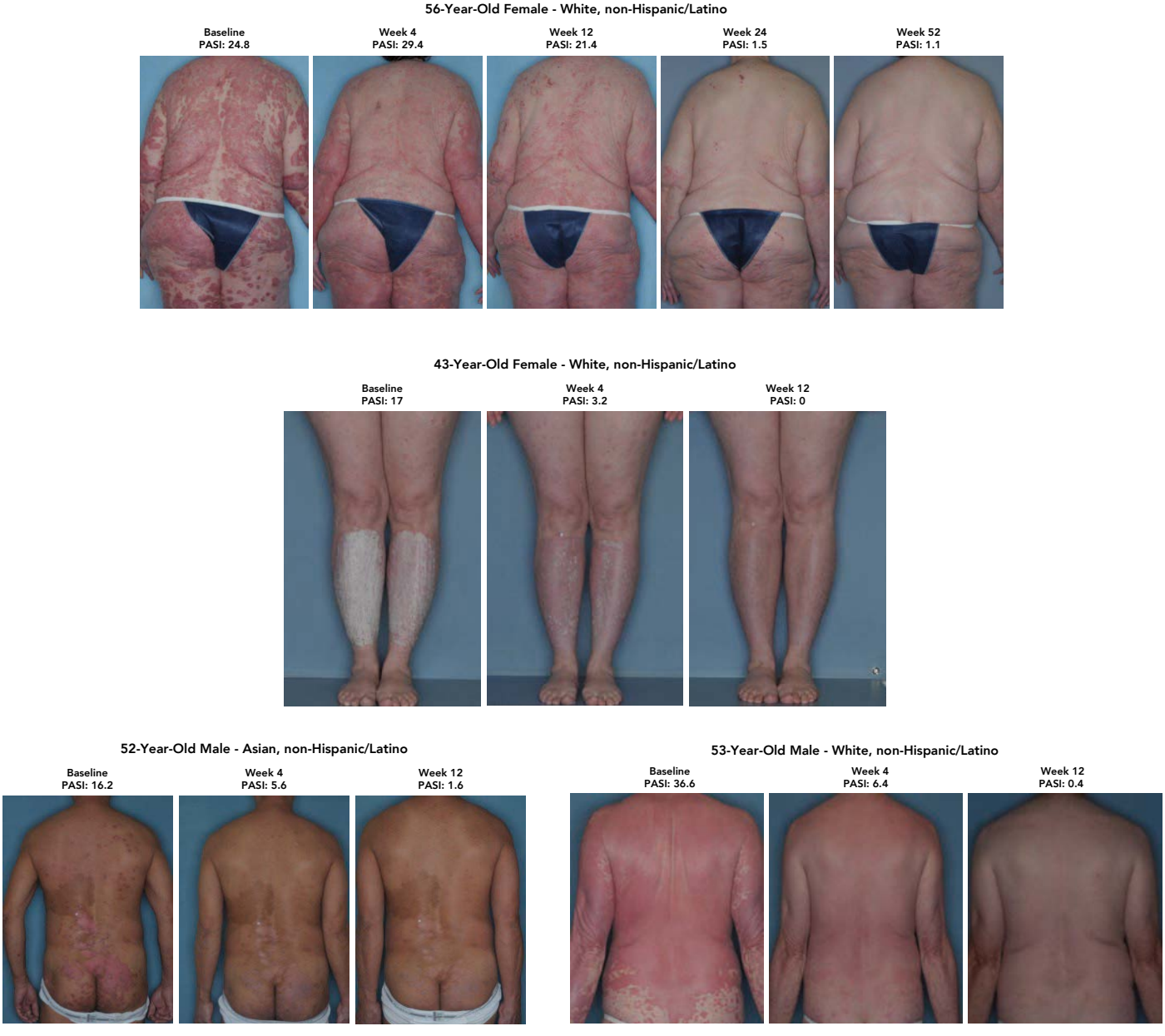
Week 52 and Week 120

Following the 12-week induction period, patients who continued to receive brodalumab during 40-week maintenance periods across the 3 pivotal trials maintained rates of PASI 75 and of sPGA 0/1 from week 12 through week 52, with additional improvements in PASI 90 and 100 rates (Table 1). Brodalumab has also demonstrated long-term efficacy following 120 weeks of continuous treatment in the phase 3 trials (Table 1).[14,15]

Importantly, of the patients treated with brodalumab achieving sPGA success (score of 0 or 1) at the end of the induction period in AMAGINE-1 who then experienced return of disease (sPGA ≥3 after week 16) upon rerandomization to placebo, 97% recaptured sPGA success after 12 weeks of retreatment with brodalumab, with a median time to sPGA success recapture of 4 weeks.[12]

Images of 4 participants treated with brodalumab from the 3 pivotal trials are shown in Figure 3.

FIGURE 3. Improvements with brodalumab in participants from the pivotal trials.



PASI, Psoriasis Area and Severity Index.

Efficacy in Patients With a History of Biologic Use

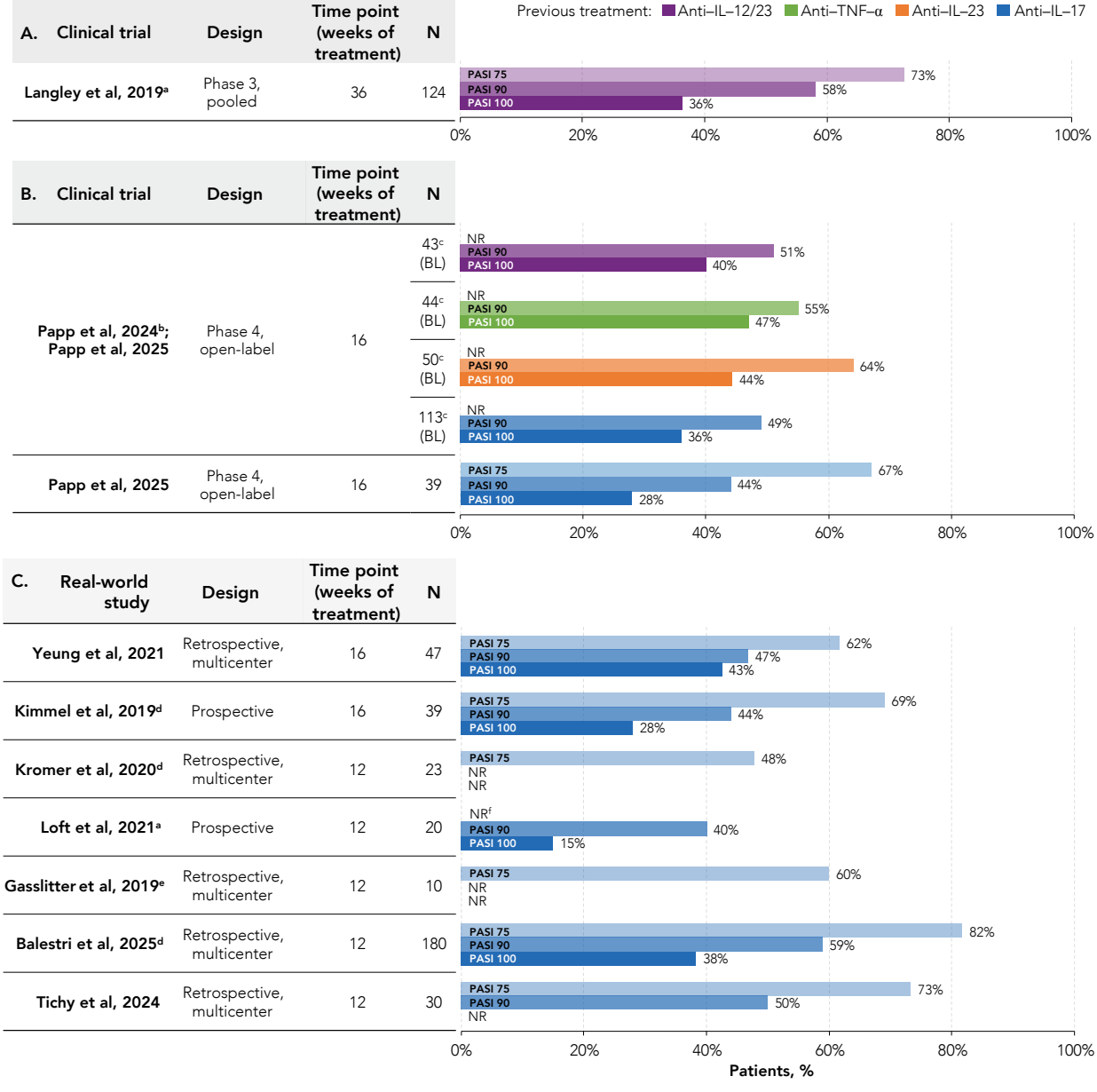
Clinical Trials

Brodalumab was efficacious in patients with psoriasis irrespective of their history of biologic use (ie, naïve or experienced).[22] In AMAGINE-2 and -3, 27% of participants treated with 210 mg brodalumab received prior biologic therapy. Brodalumab efficacy in patients with versus without previous biologic exposure was not statistically different in terms of patients achieving PASI 75 (82% vs 87%), PASI 90 (64% vs 72%), and PASI 100 (40% vs 41%) at week 12 (*P*>.05); similarly, the proportion of patients achieving sPGA of 0/1 was numerically similar between groups (74% vs 81%; no *P* value provided).

Efficacy in Patients With Inadequate Response to Other Biologics

While biologics are generally effective for treating moderate-to-severe psoriasis, some patients may fail to respond, with nonresponse to initial treatment constituting primary failure and loss of initial response to treatment as secondary failure.[10,23] Clinical trial and real-world data from patients with inadequate treatment response who switched to brodalumab from other biologics are summarized below.

FIGURE 4. PASI rates in patients who switched to brodalumab from other biologics.[5,16-21,24-26]



[a]Missing values were imputed by nonresponder imputation, which imputed missing values as nonresponse. [b]Based on observed cases. [c]Represents number of patients at baseline. [d]Missing values imputed using last observation carried forward. [e]Calculated by adding individual n/N values provided for patients switching from secukinumab to brodalumab with ixekizumab to brodalumab. [f]Only reports patients achieving PASI 75 and/or absolute PASI ≤2.
BL, baseline; NR, not reported; PASI, Psoriasis Area and Severity Index.

Clinical Trials

The AMAGINE-2 and -3 trials included an active comparator arm comprising patients randomized to treatment with ustekinumab; at week 16, patients with an inadequate response to ustekinumab could either remain on the treatment or switch to brodalumab 210 mg.[13] A post hoc analysis of these studies showed skin clearance rates at week 52 in patients switching to brodalumab starting at week 16 were numerically higher than in those who continued ustekinumab (PASI 75, 73% vs 62%; PASI 90, 58% vs 26%; PASI 100, 36% vs 5%; Figure 4A).[24] Further, from week 12 to week 52, patients who switched to brodalumab experienced a 3-fold increase in PASI 75 (24% to 73%) and an 11-fold increase in PASI 90 (5% to 58%) rates, with PASI 100 improving from 0 to 36%; similar improvement was observed in rates of sPGA score of 0/1 (data not shown).

Two phase 4, open-label, 26-week studies evaluated brodalumab in patients with moderate-to-severe psoriasis who had an inadequate response after 12 weeks of stable-dose treatment with another biologic (TNF-α, IL-12/23, IL-23, or IL-17 inhibitors).[25,26] In these studies, brodalumab demonstrated efficacy regardless of previous biologic treatment; at week 16, when stratified by biologic class, brodalumab provided PASI 90 rates ranging from 44% to 64% and PASI 100 rates ranging from 28% to 47% (Figure 4B).

Real-World Studies

Several real-world studies have demonstrated efficacy of brodalumab in patients previously treated with the IL-17A inhibitors secukinumab and/or ixekizumab (Figure 4C).[5,16-21] The 7 studies reviewed here were prospective or retrospective in design, with numbers of patients evaluated ranging from 10 to 180, and PASI rates recorded at week 12 or week 16. In the studies reporting brodalumab efficacy at week 16, PASI 75 rates were 62% and 69%, PASI 90 rates were 47% and 44%, and PASI 100 rates were 43% and 28%. In the studies reporting efficacy at week 12, PASI 75 was achieved by 48%–82% of patients, PASI 90 was achieved by 40%–59%, and PASI 100 rates were 38% and 15%.

Efficacy in Other Key Subgroups

Scalp and Nail Psoriasis

Psoriasis can affect both the scalp and the nails, with scalp and nail involvement estimated to occur in nearly 80% and 50% of people with psoriasis, respectively.[27,28] Psoriasis of both the scalp and nail can be difficult to treat—the presence of hair can impair correct topical treatment application or penetration, and the slow growth of nails can cause psoriasis to persist for extended periods of time.[29]

Scalp clearance and nail clearance efficacy of brodalumab were evaluated in the phase 3 AMAGINE-1 and AMAGINE-2/-3 trials, respectively.[29] At week 12, 89% of patients treated with brodalumab achieved at least 75% improvement from baseline in the Psoriasis Scalp Severity Index (PSSI 75) and 63% achieved PASI 100, which were significantly greater than with placebo (P<.001, both). The percentage of patients with complete clearance of nail psoriasis (Nail Psoriasis Severity Index [NAPSI] 0) at weeks 12 and 52 were significantly greater with brodalumab versus ustekinumab (week 12, 8% vs 2%; week 52, 64% vs 39%; P<.05, both). Overall, brodalumab was effective for treatment of scalp and nail psoriasis.

Body Mass Index

Obesity is known to increase the risk of psoriasis and can influence response to therapy.[30,31] A post hoc analysis of the AMAGINE-2 and -3 trials demonstrated that the efficacy of brodalumab did not markedly differ between nonobese (body mass index [BMI] <30 kg/m^2) and obese (BMI ≥30 kg/m^2) patients with psoriasis.[31] Skin clearance was comparable across BMI subgroups in patients treated with brodalumab. For example, PASI 100 rates in nonobese and obese patients were 54% and 50%, respectively, at week 12 and were 73% and 65% at week 52. Further, week 12 PASI 100 rates in both nonobese and obese patients treated with ustekinumab (37% and 24%, respectively) were significantly lower than their respective brodalumab-treated counterparts (P≤.002, both).

Safety

Clinical Trials

An integrated analysis of 5 brodalumab clinical trials evaluated safety across patients who had continuously received brodalumab, placebo, or the active comparator ustekinumab.[32] Rates of serious adverse events (AEs) per 100 patient-years were slightly higher in the brodalumab group compared with ustekinumab and placebo in the 12-week induction period (9.6 vs 4.3 and 6.5, respectively) and versus ustekinumab over the entire 52-week trial period (10.1 vs 8.3). Study and drug discontinuations were low in the brodalumab group (≤5.2%) over 52 weeks, but slightly higher compared with ustekinumab (≤2.1%).

The most frequently reported treatment-emergent AEs (≥3%) included upper respiratory tract infection, nasopharyngitis, headache, and arthralgia. AEs of special interest in the brodalumab group over the 52-week period included infections (serious and fungal), Crohn's disease, neutropenia, major adverse cardiac events, malignancies, and hypersensitivity. Of these, infections were the most frequent, occurring in 54.6% of patients on brodalumab; the remaining AEs of special interest all occurred at low rates not different from the ustekinumab group (0.2%–3.9% vs 0%–6.4%).[32]

There were 4 suicide events in the brodalumab group during the 52-week period; all 4 patients had confounding factors, including stressors or a history of depression, and no events could conclusively be linked to treatment. As such, there is no established causal link between brodalumab treatment and increased risk of suicidal ideation or behavior.[32] Further, a post

hoc analysis of psychiatric AEs across these 5 brodalumab clinical trials found the psychiatric AE rates in patients treated with brodalumab were similar to those in patients receiving 12 weeks of placebo and in patients receiving 12 or 52 weeks of ustekinumab.[33] Additionally, the rate of suicidal ideation and behavior events with brodalumab was similar to that of placebo or ustekinumab during the 12-week induction phase and comparable to ustekinumab during the first year of treatment. Finally, it is important to note that while most clinical trials of systemic drugs for moderate-to-severe psoriasis have specific exclusion criteria for psychiatric disorders or substance abuse, the AMAGINE trials did not include such criteria.[33]

Overall, brodalumab was well tolerated and was not associated with an increased risk of malignancy, major adverse cardiac events, suicidal ideation and behavior, or fatal AEs.

8-Year Pharmacovigilance Report

Pharmacovigilance data reported by US patients and healthcare providers to Ortho Dermatologics (a division of Bausch Health Companies, Inc.) have been published on a yearly basis.[34-40] To examine safety data over 8 years of clinical usage, here we evaluate reported AEs during the period spanning from August 15, 2017 to August 14, 2025.

Detailed methods have been described in previously published pharmacovigilance reports.[34-40] In brief, for AEs listed in the package insert (those occurring in ≥1% of patients) and other events of special interest, crude AE reporting rates per 100 patients were calculated using Medical Dictionary for Regulatory Activities (MedDRA) v28.0 Preferred Terms and standardized MedDRA queries; these are summarized using descriptive statistics. Treatment duration was determined by measuring the time between the initial and latest prescription-dispensing authorization dates. As all data are nonidentifiable, ethical approval and informed consent were not required.

Where applicable, crude AE reporting rates of cases with events of interest have been indirectly compared to those calculated from the Psoriasis Longitudinal Assessment and Registry (PSOLAR), an intercontinental registry including 12,095 patients with psoriasis receiving or eligible to receive biologic or systemic therapy, inclusive of, but not limited to, infliximab, ustekinumab, golimumab, adalimumab, etanercept, alefacept, efalizumab, and nonbiologic systemic agents such as methotrexate (median follow-up, 2.5 years; estimated follow-up, 31,818 patient-years).[34,41,42] Crude AE reporting rates of cases with events of interest from PSOLAR were calculated by dividing the number of events by the number of patients (12,095) and multiplying by 100, with the assumption that the numbers of cases and events were equal.

The brodalumab analysis encompassed 5,654 patients from the US, representing approximately 8,647 patient-years of exposure across the 8-year reporting period. Over this period, 2,908 patients had at least 1 reported case of unique AE, with 24.6% of AEs reported by healthcare professionals.

In the brodalumab package insert, common AEs listed include arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection-site reactions, influenza, neutropenia, and *Tinea* infections.[4] Other AEs that have been deemed of special interest by the reporter or company include adjudicated major adverse cardiovascular events (MACEs), serious infections, fungal infections, inflammatory bowel disease (IBD), malignancy, depression, and completed suicide. Crude AE reporting rates per 100 patients of the most common AEs listed in the brodalumab package insert and AEs of special interest are shown in Figure 5A. Arthralgia remained the most frequently reported common AE (crude AE reporting rate per 100 patients, 2.58), consistent with previous findings. Serious infection was the most frequently reported AEs of special interest (2.14). For the AEs of special interest of adjudicated MACE, malignancy, and serious infections, 8-year rates per 100 patients with brodalumab were lower than those calculated from the PSOLAR registry (adjudicated MACE, 0.25 vs 0.94; malignancy [excluding nonmelanoma skin cancer in PSOLAR], 1.13 vs 1.78; serious infections, 2.14 vs 3.95).

New cases of AEs and AEs of special interest reported in year 8 are detailed in Figure 5B. New cases of common AEs reported in year 8 ranged from 0 (*Tinea* infections, neutropenia, oropharyngeal pain, and influenza) to 6 (arthralgia). New cases of AEs of special interest reported in year 8 ranged from 0 (completed suicide, IBD, fungal infection) to 11 (malignancy).

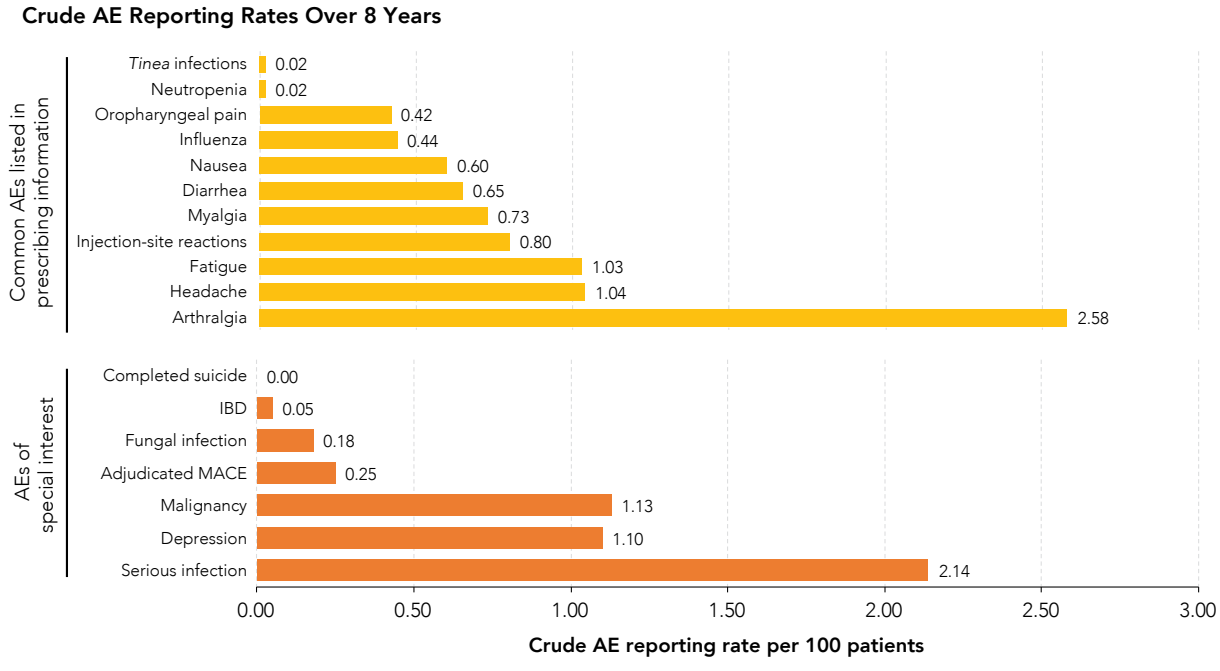
Although 3 new cases of serious infections were reported in year 8, no new cases of *Candida* infections or deaths due to COVID-19 were reported.

The new cases of malignancies in year 8 (n=11) were reported in 9 patients. Types of reported malignancies included malignant melanoma (n=2), squamous skin cancer (n=1), non-melanoma skin cancer (basal cell [n=3] and squamous cell [n=4]), and prostate cancer (n=1). Of the 9 new patients who reported cases of malignancy, none were deemed related to brodalumab and 3 patients continued brodalumab treatment.

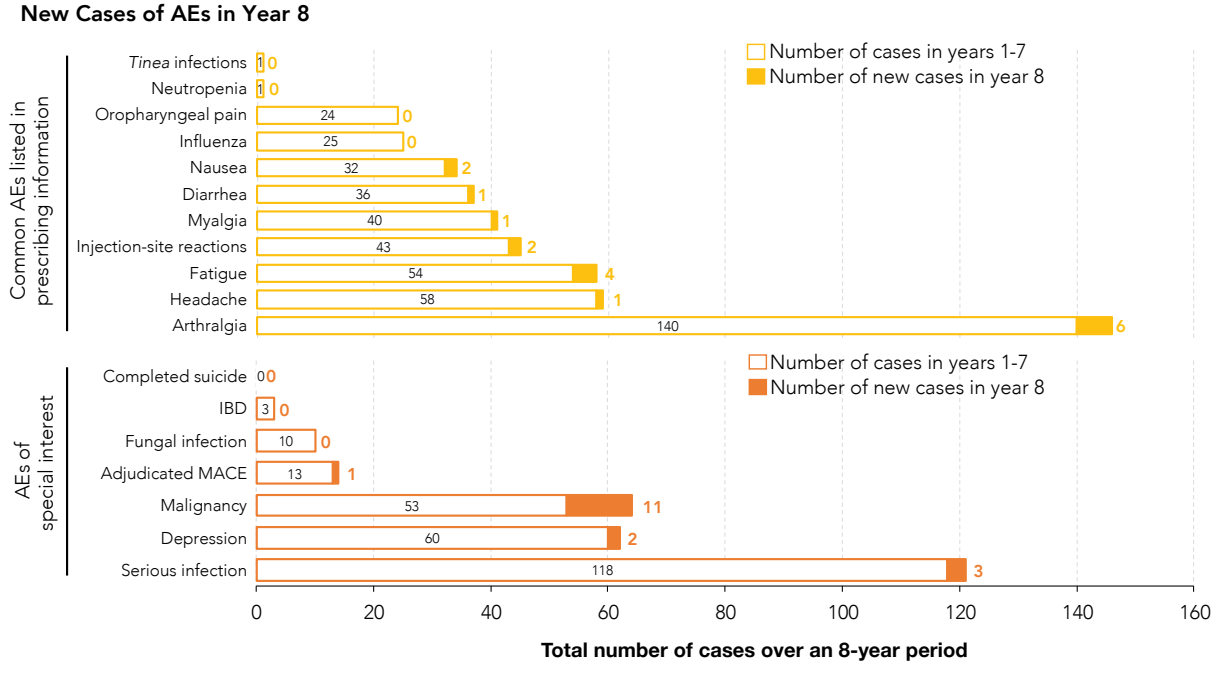
One new case of adjudicated MACE occurred in year 8. Over the 8-year period, 14 cases of adjudicated MACE have been reported, including myocardial infarction (n=6), stroke (n=1), ischemic coronary artery bypass procedure (n=1), coronary artery disease requiring a stent (n=1), and transient ischemic attack (n=1). Of these 14 reported cases, 13 (92.8%) included patients who had a known history of cardiovascular-associated risk factors/ pre-existing conditions or documented relevant concomitant medications.

FIGURE 5. Eight-year pharmacovigilance safety profile of brodalumab.

(A)



(B)



Crude AE reporting rate per 100 patients is the number of cases with clinical events of special interest divided by total number of patients and multiplied by 100. Analysis accounts for the possibility that a single patient may report multiple cases of an AE. Prevalence of most common AEs was defined in the brodalumab package insert as incidence ≥1%.[4] Clinical events of special interest were defined using MedDRA v28.0 terms. Serious infection (ie, prolonged infection or infection requiring intervention) included any MedDRA preferred term (PT) identified under the system organ class (SOC) name "Infections and infestations," for which the SOC was indicated as "primary" and event seriousness as "serious." Depression included MedDRA PTs from "Depression" (excluding "Suicide" and "Self-injury") standardized MedDRA queries (SMQ; narrow). Malignancy included MedDRA PTs from "Malignancies" SMQ and "Malignant lymphomas" SMQ. Adjudicated MACE included MedDRA PTs from "Ischemic CNS vascular conditions" SMQ, "Ischemic heart disease" SMQ ("Myocardial infarction"), and "Ischemic heart disease" SMQ ("Other"), and where "medically confirmed" was blank. Fungal infection included MedDRA HLTs from "Fungal infections" NEC. Inflammatory bowel disease included MedDRA PTs "Inflammatory bowel disease," "Irritable bowel syndrome," "Crohn's disease," and "Colitis ulcerative."[34]

AE, adverse event; CNS, central nervous system; HLT, high level term; IBD, irritable bowel disease; MACE, major adverse cardiovascular event; NEC, not elsewhere classified; PT, preferred term.

Two new cases of depression were documented in year 8 (n=1 no causality assessment provided, n=1 deemed not related to brodalumab). No new suicide attempts or complete suicides were reported in year 8, 1 suicide attempt was previously reported in year 3,[34] and no completed suicides were reported throughout the 8 years. The reporting physician of the suicide attempt in year 3 did not indicate any suspected causal relationship between brodalumab and the depressed mood or self-harm attempt; the patient had a history of depression.[34]

This 8-year pharmacovigilance dataset reinforces the safety profile of brodalumab previously established through clinical trials and earlier pharmacovigilance reports, with no completed suicides and a low fungal infection rate.

Brodalumab and the Risk Evaluation and Mitigation Strategies Program

Brodalumab is available in the US only through a Risk Evaluation and Mitigation Strategies (REMS) program—a drug safety program from the US Food and Drug Administration—due to the risk of suicidal ideation and behavior, including completed suicides, observed in its clinical trials.[4] Healthcare professionals who wish to prescribe brodalumab must be certified in the REMS program, and their patients must enroll to obtain their prescriptions.[43] A recent call to action[44] drafted by a psoriasis expert consensus panel called into question the need for this monitoring program on the grounds that (i) the 4 participants who committed suicide in the brodalumab trials were noted to have preexisting psychiatric disorders and significant life stressors, such as marked financial instability, (ii) the brodalumab clinical trials did not exclude patients with clinically significant neuropsychiatric disease and active substance abuse, in contrast with some previous psoriasis studies, and (iii) pharmacovigilance data from thousands of patients treated with brodalumab do not support an association between brodalumab and depression or suicidal ideation and behavior. The authors concluded that brodalumab may be underutilized because of this monitoring program.

CONCLUSION

Brodalumab has now accumulated a substantial body of evidence supporting its role as an effective and durable treatment for moderate-to-severe plaque psoriasis. Across clinical trials and real-world studies, brodalumab consistently delivered rapid skin clearance, high rates of complete response, and sustained disease control, even among patients who had not achieved adequate benefit with other biologics. Its unique mechanism of action targeting the IL-17 receptor A and blocking signaling from multiple IL-17 isoforms provides a biological basis for its strong clinical performance. Eight years of pharmacovigilance experience further affirm a stable safety profile, with no emerging safety signals and no demonstrated causal link to increased psychiatric events. Taken together, these findings reinforce that brodalumab is an important therapeutic option for achieving high levels of disease control in patients with moderate-to-severe psoriasis, including those with prior biologic exposure or difficult-to-treat disease manifestations. Its distinct mechanism and durable efficacy support its continued and potentially broader use within the evolving psoriasis treatment landscape.

DISCLOSURES

Mark G. Lebwohl is an employee of Mount Sinai and has received research funds from AbbVie, Arcutis, Avotres, Boehringer Ingelheim, Bristol Meyers Squibb, Cara Therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Johnson & Johnson, Oruka, Pfizer, Sanofi-Regeneron, and UCB, and is 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, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Galderma, Genentech, Incyte, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Meiji Seika Pharma, Moonlake, Oruka, Pfizer, Sanofi-Regeneron, Revolo, Seanergy, Strata, Sun Pharma, Takeda, Trevi, and Verrica. James G. Krueger has received grant support (to The Rockefeller University) from AbbVie, Amgen, Artax Biopharma, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Bruxelles Biopharma, Exicure, Innovaderm, Incyte, Janssen, Kyowa Kirin, Lilly, Novan, Novartis, ONO Pharmaceutical, Oruka, Pfizer, Provectus, Regeneron, SUDO Bio, Takeda, UCB, Vitae Pharmaceuticals, Ventyx (Zomagen); consulting fees from AbbVie, Allergan, Almirall, Amgen, Artax Biopharma, Aristea, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Calliditas, Citryll, CSL Behring, Eli Lilly, Escalier, Evommune, Incyte, Immunitas Therapeutics, Janssen, Kymera Therapeutics, Kyowa Kirin, MC2 Therapeutics, Merck, MoonLake Immunotherapeutics, Navigator, Novartis, Nuvig Therapeutics, Oruka Therapeutics, Pfizer, Sanofi, Schrodinger, Sun Pharma, Takeda, Target Derm, UCB, UNION Therapeutics, Valeant, and Ventyx. John Y. Koo has served as a speaker for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Galderma, Leo Pharma, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB and as a consultant for Castle, Janssen, and Sun Pharma. George Han has received honoraria or research grants from AbbVie, Alumis, Amgen, Arcutis, Athenex, Bausch Health, Boehringer Ingelheim, Bond Avillion, Bristol Myers Squibb, Celgene Corporation, Dermavant, DermTech, Eli Lilly and Company, EPI Health, Janssen Pharmaceuticals, LEO Pharma, MC2 Therapeutics, Novartis, Ortho Dermatologics, PellePharm, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, SUN Pharmaceutical Industries Ltd, and UCB. April W. Armstrong has served as research investigator and/or consultant to AbbVie, Janssen, Lilly, LEO Pharma, Novartis, UCB, Ortho Dermatologics, Dermira, Sanofi, Regeneron, Bristol Myers Squibb, Dermavant, and Modernizing Medicine. Bruce E. Strober has served as consultant, investigator, or speaker for

AbbVie, Alumis, Almirall, Amgen, Apogee, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, CorEvitas Psoriasis and GPP registries, Dermavant, Immunovant, Incyte, Janssen, Johnson & Johnson, Leo, Eli Lilly, Maruho, Neurocrine, Novartis, Oruka, Meiji Seika Pharma, Protagonist, Pfizer and UCB; Pharma, Rapt, Regeneron, Sanofi-Genzyme, SelectION and Takeda; holds stock options in Mindera Health and SelectION; and is scientific co-director (consulting fee) for CorEvitas Psoriasis Registry. Leon H. Kircik has served as a consultant, speaker, advisor, or investigator for and has received grant funding or honoraria from Abbott Laboratories, AbbVie, Allergan, Inc., Almirall, Amgen, Inc., Arcutis, Biogen-Idec, Bristol Myers Squibb, Boehringer-Ingleheim, Breckinridge Pharma, Celgene, Centocor, Inc., Cellceutix, Cipher, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Eli Lilly, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Idera, Johnson & Johnson, Leo, Maruho, Merck, Medicis Pharmaceutical Corp., Nimbus, Novartis AG, Promius, PharmaDerm, Pfizer, Serono (Merck Serono International SA), Stiefel Laboratories, Inc., Sun Pharma, Taro, UCB, Valeant Pharmaceuticals Intl, Ventyx, and XenoPort.

ACKNOWLEDGMENT

Medical writing support was provided by Kavitha Abiraman PhD from Citrus Health Group, Inc. (Chicago, Illinois), with financial support from Ortho Dermatologics. Ortho Dermatologics is a division of Bausch Health US, LLC.

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doi:10.36849/JDD.9806

March 2026 221 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Advanced Topical Nonsteroidal Therapies for Atopic Dermatitis: Consensus Statements From an Expert Panel

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ABSTRACT

Background: Advanced topical nonsteroidal therapies are expanding options for atopic dermatitis (AD) by providing targeted anti-inflammatory control without many limitations of long-term topical corticosteroids. As these agents become more available, practical guidance is needed on their use as first-line therapy, proactive maintenance, combination regimens, safety, and long-term management.
Objective: To develop expert consensus statements defining the clinical role of advanced topical nonsteroidal therapies in AD.
Methods: A seven-dermatologist expert panel used a structured Delphi process informed by a literature review. Statements were drafted, iteratively refined, and voted on across multiple rounds. Evidence quality and strength of recommendations were assessed using the Strength of Recommendation Taxonomy (SORT). Consensus was predefined as ≥75% agreement.
Results: The panel reached unanimous consensus on seven statements regarding advanced topical nonsteroidal therapies, including topical ruxolitinib, tapinarof, roflumilast, crisaborole, tacrolimus, pimecrolimus, and delgocitinib. These therapies were considered effective in reducing AD signs and symptoms, including pruritus, and appropriate as first-line agents for many patients. Their use was associated with longer disease control, fewer relapses, and reduced cumulative topical corticosteroid exposure. The panel agreed that these therapies improve patient-reported outcomes, including quality of life and sleep, and can be safely incorporated into combination regimens with other topical or systemic treatments. They demonstrated favorable safety and tolerability profiles without the need for baseline or ongoing laboratory monitoring. Compared with topical corticosteroids, nonsteroidal therapies were preferred for long-term management to avoid steroid-associated adverse effects, with simplified dosing and suitability for sensitive and high-impact sites supporting adherence.
Conclusion: Advanced topical nonsteroidal therapies represent an important evolution in AD management and are appropriate first-line options across disease severities, supporting sustained disease control and improved quality of life.

J Drugs Dermatol. 2026;25(3):221-227. doi:10.36849/JDD.9806

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that imposes a substantial burden through persistent itch, sleep disturbance, and impaired quality of life. Despite major advances in systemic therapy, topical treatment remains central to AD management across disease severities, serving as first-line therapy for mild disease and as adjunctive treatment for residual activity in patients receiving systemic agents. Because AD often involves sensitive anatomic sites and requires consistent and/or long-term treatment, the safety and durability of topical therapies are critical considerations in routine practice.

The long-term use of topical corticosteroids (TCS) is limited by cutaneous and systemic risks, as well as by adherence challenges. Steroid-sparing options such as topical calcineurin inhibitors (TCI) have addressed some of these limitations, though their clinical effect may be modest for certain patients. More recently, advanced topical nonsteroidal therapies, including topical Janus kinase (JAK) inhibitors, aryl hydrocarbon receptor agonists, and phosphodiesterase-4 (PDE4) inhibitors, have expanded the therapeutic landscape (Table 1).

TABLE 1.

Nonsteroidal Agents for Atopic Dermatitis

Medication	Mechanism of Action	FDA Approval Status for AD	Formulation Strength
Ruxolitinib	Inhibits JAK1 and JAK2	Yes	Cream, 1.5%, Applied twice daily
Tapinarof	Aryl-hydrocarbon receptor agonist	Yes	Cream, 1%, Applied once daily
Roflumilast	Phosphodiesterase-4 (PDE-4) inhibitor	Yes	Cream, 0.15% or 0.05%, Applied once daily
Crisaborole	Phosphodiesterase-4 (PDE-4) inhibitor	Yes	Ointment, 2%, Applied twice daily
Pimecrolimus	Calcineurin inhibitor; blocks T-cell activation by binding to FKBP-12	Yes	Cream, 1%, Applied twice daily
Tacrolimus	Calcineurin inhibitor; blocks T-cell activation by binding to FK506 binding protein	Yes	Ointment, 0.03% and 0.1%, Applied twice daily
Delgocitinib	Pan JAK inhibitor: Inhibits JAK1, JAK2, JAK3, and TYK2 enzymes	No	Cream, 2%, Applied twice daily*

Abbreviations: *Approved for chronic hand eczema; FDA, Food and Drug Administration; FKBP-12, FK506-binding protein-12; N/A, not applicable; JAK, janus kinase inhibitor; PDE-4, phosphodiesterase-4; TYK2, tyrosine kinase-2

With the growing availability of these agents, clinicians are increasingly faced with questions regarding patient selection, positioning within treatment algorithms, use for proactive maintenance, and combination with other topical or systemic therapies. This consensus document brings together available evidence and expert clinical experience to provide practical guidance on the role of advanced topical nonsteroidal therapies in the management of AD.

MATERIALS AND METHODS

A panel of seven dermatologists with expertise in inflammatory dermatoses and topical therapeutics was assembled to generate evidence-based consensus statements regarding the use of advanced topical nonsteroidal therapies for AD (AWA, CGB, RC, AAH, LK, JY, MGL). Panel members were selected based on their clinical experience and scholarly contributions across a range of practice settings.

A Delphi process was employed, beginning with a structured literature review (by YN) followed by independent evaluation of the contributing evidence by each panelist. Studies were appraised according to quality, consistency, and clinical relevance. Recommendations were developed using the Strength of Recommendation Taxonomy (SORT) framework to evaluate the available evidence.[1] Draft statements were then refined and rated through standardized Delphi rounds. Consensus was predefined as agreement by at least 75% of panel members, and only statements meeting this criterion were included in the final set of recommendations.

RESULTS

The expert panel reached consensus on seven key statements addressing the role of advanced topical nonsteroidal therapies in AD. These statements summarize the available evidence and provide practical guidance for clinicians managing this heterogeneous and burdensome condition (Table 2).

Statement 1: Advanced topical nonsteroidal therapies reduce signs and symptoms of AD, including itch, and are appropriate first-line agents for managing atopic dermatitis.

Newer topical nonsteroidal therapies for AD, including ruxolitinib, tapinarof, roflumilast, and crisaborole, provide effective steroid-sparing options that can be used across patient ages and severities of disease. For example, multiple randomized controlled trials have shown that topical ruxolitinib (a JAK inhibitor),[2-14] tapinarof (an aryl hydrocarbon receptor agonist),[15-22] and the PDE-4 inhibitors roflumilast[23-25] and crisaborole[26-37] are effective nonsteroidal options for improving patient-reported symptoms, itch, and clinician-assessed signs, with rapid relief of itch and improvements in quality of life. These agents are effective in both the adult and pediatric populations. For example, tapinarof and roflumilast are approved for use in adults and children aged 2 years and older, and crisaborole for infants as young as 3 months.[38-40] Topical nonsteroidal therapies are increasingly valued because they meaningfully reduce inflammation, visible signs, and itch while avoiding the risks associated with prolonged corticosteroid exposure, making them appropriate first-line options for many patients with mild to moderate AD.

TABLE 2.

Consensus Statements for Atopic Dermatitis

Statement	Strength of Recommendation	Consensus Vote
Statement 1: Advanced topical nonsteroidal therapies reduce signs and symptoms of atopic dermatitis, including itch, and are appropriate first-line agents for managing atopic dermatitis.	A	7/7
Statement 2: The use of advanced topical nonsteroidal therapies prolongs off-treatment disease control, reduces relapses, and decreases cumulative corticosteroid exposure in atopic dermatitis.	A	7/7
Statement 3: Advanced topical nonsteroidal therapies improve quality of life and sleep in patients with atopic dermatitis.	A	7/7
Statement 4: Advanced topical nonsteroidal therapies can be used in combination with other topical or systemic therapies for management of atopic dermatitis.	C	7/7
Statement 5: Advanced topical nonsteroidal therapies are safe, well-tolerated, and do not require laboratory workup prior to or during treatment.	A	7/7
Statement 6: Advanced topical nonsteroidal therapies are preferred for long-term management of atopic dermatitis over topical corticosteroids because nonsteroidal therapies avoid corticosteroid-associated adverse events.	C	7/7
Statement 7: Advanced topical nonsteroidal therapies offer greater convenience and adherence over topical corticosteroids for treatment of atopic dermatitis.	C	7/7

While TCS are used commonly for AD management, they carry risks when used over large body surface areas or for extended durations, including systemic absorption and hypothalamic–pituitary–adrenal (HPA) axis suppression, concerns that are heightened in young children and with occlusion.[14,41-43] As a result, nonsteroidal therapies are often preferred for sensitive areas, for intermittent maintenance, and in situations where systemic therapies are contraindicated or not tolerated.[2,13,18,23-25,32] For patients with extensive and chronic disease, topical therapy may provide partial or temporary control, but systemic treatment is frequently required, with topical agents still needed for breakthrough flares.[28,44-46] Topical calcineurin inhibitors also remain available as steroid-sparing agents, although their clinical effect tends to be more modest than that of the newer nonsteroidal therapies.[47] Overall, most patients with limited AD can be effectively managed with an appropriate regimen that prioritizes safe, well-tolerated, and topical nonsteroidal options.

Statement 2: The use of advanced topical nonsteroidal therapies prolongs off-treatment disease control, reduces relapses, and decreases cumulative corticosteroid exposure in atopic dermatitis.

Advanced topical nonsteroidal therapies such as tapinarof, ruxolitinib, roflumilast, and crisaborole contribute meaningfully to sustained disease control in AD by reducing signs and symptoms, stabilizing the skin barrier, and suppressing the subclinical inflammation that drives recurrent flares.[6,9,27,28] Because these agents can be used safely for longer durations than topical corticosteroids, they help maintain disease control, extend flare-free intervals while lowering cumulative steroid exposure over time.[6,28,48]

For example, tapinarof has demonstrated a remittive effect in AD, with ADORING 3 showing a mean first treatment-free interval of 79.8 consecutive days after achieving complete clearance (vIGA-AD=0).[49] Roflumilast also supports proactive maintenance, with INTEGUMENT-OLE data showing that patients who reached vIGA-AD 0 and transitioned to twice-weekly proactive application maintained vIGA-AD 0/1 for a median of 281 days (Kaplan–Meier estimate).[50] Ruxolitinib cream has demonstrated durable disease control with as-needed use over 44 weeks, with 74.1%–77.8% achieving IGA 0/1 at week 52 and low mean affected BSA (1.4%–1.8%).[9] Crisaborole has also shown benefit as maintenance therapy, with once-daily crisaborole extending median flare-free time (111 vs 30 days) and reducing mean flares (0.95 vs 1.36) versus vehicle over 52 weeks.[28] Together, these therapies offer durable disease control that decreases reliance on repeated steroid courses.

These advantages align with the principles of proactive therapy, which involves low-frequency application to previously affected areas to suppress subclinical inflammation and maintain remission.[51] Owing to their favorable safety profiles with prolonged or repeated use, advanced topical nonsteroidal therapies, including tapinarof, ruxolitinib, roflumilast, crisaborole, and topical calcineurin inhibitors, are well-suited for proactive maintenance, reducing relapse frequency, limiting the need for repeated corticosteroid courses, and lowering cumulative corticosteroid exposure in AD.

Statement 3: Advanced topical nonsteroidal therapies improve quality of life and sleep in patients with atopic dermatitis.

The impact of AD extends beyond visible skin lesions, with itch, sleep disturbance, and impaired daily functioning representing some of the most disruptive aspects of the disease. Advanced topical nonsteroidal therapies such as tapinarof, ruxolitinib, roflumilast, and crisaborole contribute meaningfully to improvements in these patient-centered outcomes by targeting the underlying inflammatory pathways that drive pruritus and nocturnal symptoms.[8,12,19,23,25,34] Rapid reductions in itch are particularly important, as the itch–scratch cycle perpetuates inflammation, interferes with sleep continuity, and contributes to daytime fatigue, mood disturbance, and reduced productivity.[3,8,22,34,37,52] In addition to pruritus and sleep disturbance, AD patients frequently experience skin pain and burning, and advanced topical nonsteroidal therapies may reduce these symptoms by attenuating cutaneous inflammation and neural sensitization.

Across clinical trials, advanced topical nonsteroidal therapies have demonstrated rapid onset of itch relief, with improvements observed within days to weeks of treatment initiation, supporting their clinically meaningful impact on early symptom control. For example, ruxolitinib provides rapid relief of itch, and reductions in pruritus have been associated with improvements in sleep disturbance scores, reflecting less nocturnal scratching and greater nighttime comfort.[3,4,8,12] Roflumilast and crisaborole also contribute to symptom reduction in areas such as the face and intertriginous skin, where discomfort and visibility can have meaningful effects.[23-25,30,32,36,37] Tapinarof has also been shown to improve quality-of-life measures.[17,19,21,22] By reducing flares, stabilizing disease activity, and easing symptoms, advanced topical nonsteroidal therapies improve sleep, daily functioning, and overall quality of life for individuals with AD and their families.

Statement 4: Advanced topical nonsteroidal therapies can be used in combination with other topical or systemic therapies for management of atopic dermatitis.

Advanced topical nonsteroidal therapies can be effectively incorporated into combination regimens across different severities of AD. Published clinical experience highlight that these agents integrate well alongside both topical and systemic treatments.[53] Their favorable safety profiles and targeted mechanisms of action allow them to be used concurrently with other topical therapies and systemic agents such as biologics or JAK inhibitors when additional symptom control is needed.
In clinical practice, combination approaches are commonly used to address regional variability in disease expression, accelerate clearance during flares, and provide symptom relief while systemic therapies take effect. Topical nonsteroidal agents may be applied to sensitive or high-impact areas while systemic therapies manage broader disease activity, or they may be combined with intermittent corticosteroid use. Advanced topical nonsteroidals can also support tapering strategies by maintaining control as other therapies are withdrawn.

Because advanced topical nonsteroidal therapies reduce inflammation, itch, and barrier disruption without adding cumulative steroid exposure, these therapies serve as versatile components of individualized treatment plans. Their compatibility with other therapeutic classes enables clinicians to optimize efficacy, enhance patient comfort, and maintain long-term disease stability.

Statement 5: Advanced topical nonsteroidal therapies are safe, well-tolerated, and do not require laboratory workup prior to or during treatment.

Advanced topical nonsteroidal therapies have demonstrated strong safety and tolerability profiles across clinical trials and real-world studies, supporting their use without the need for baseline or ongoing laboratory monitoring. Agents such as tapinarof, ruxolitinib, roflumilast, and crisaborole have consistently shown low rates of adverse events, reflecting their mechanisms of action and minimal systemic absorption.[10,24,49] Although the ruxolitinib label includes class-based JAK warnings, topical ruxolitinib does not require routine laboratory monitoring in real-world dermatology practice, as clinical studies and postmarketing experience have not shown systemic laboratory abnormalities or safety signals that would necessitate ongoing lab assessment.[6,9,10]

In pivotal trials, most adverse events associated with these therapies were mild and localized, such as transient application-site reactions, and rarely led to treatment discontinuation.[10,21,23-25,54] Their cosmetic acceptability, ease of application, and favorable tolerability also support adherence, which is essential for long-term disease control in AD. These characteristics allow clinicians to confidently initiate therapy in a broad range of patients, including children, individuals with comorbidities, and those for whom systemic monitoring is burdensome or impractical.

Statement 6: Advanced topical nonsteroidal therapies are preferred for long-term management of atopic dermatitis over topical corticosteroids because nonsteroidal therapies avoid corticosteroid-associated adverse events.

Long-term management of AD has traditionally relied on topical corticosteroids, but chronic or inappropriate use is associated with a range of well-recognized adverse effects. These include cutaneous atrophy, telangiectasia, striae, dyspigmentation, easy bruising, barrier fragility, and delayed wound healing.[55-59] Use over large body surface areas or under occlusion increases the risk of systemic absorption, which can lead to HPA axis suppression.[41-43] Ocular complications such as glaucoma and

cataracts have also been reported with prolonged periocular application.[60] Although higher-potency corticosteroids carry the greatest risk, mid- and low-potency agents are not risk-free, and adverse effects can occur with repeated or extended use regardless of strength, particularly in children and in areas with inherently thin skin.[59]

Advanced topical nonsteroidal therapies offer an alternative approach that avoids these corticosteroid-related limitations. Agents such as ruxolitinib, roflumilast, tapinarof, crisaborole, and topical calcineurin inhibitors can be used safely on sensitive areas and for prolonged intervals without concerns regarding skin thinning or systemic endocrine effects.[2,5,6,9,13,15,16,18,23,24,30,32,61] Their favorable tolerability profiles allow clinicians to apply them consistently as a part of a simplified long-term regimen, reducing the need for rotating potencies or limiting treatment duration.[2,13,18] This predictable safety enables adherence and supports the proactive maintenance strategies increasingly recommended for chronic disease control.

Statement 7: Advanced topical nonsteroidal therapies offer greater convenience and adherence over topical corticosteroids for treatment of atopic dermatitis.

Advanced topical nonsteroidal therapies provide practical advantages that can meaningfully enhance treatment convenience and adherence for individuals with AD. Unlike topical corticosteroids, these agents can be used across multiple body sites, including the face, eyelids, perioral region, and intertriginous areas, without concerns about steroid-associated adverse effects such as glaucoma, striae, steroid-induced acne, periorificial dermatitis, dyspigmentation, or progressive skin atrophy.[2,13,18] This flexibility simplifies treatment for patients with widespread or multifocal disease and reduces the need to alternate products based on anatomic location.

Many nonsteroidal agents also offer convenient dosing schedules, including once-daily regimens (example: topical tapinarof and roflumilast), which help support adherence and reduce day-to-day treatment burden.[2,21,23,24] By contrast, long-term corticosteroid regimens often require careful planning, including cycling between potencies, tapering schedules, and avoidance of certain high-risk sites.[62] These complexities can contribute to treatment fatigue, confusion, and inconsistent use.

Nonsteroidal agents also reduce polypharmacy by limiting the need for multiple corticosteroid strengths, vehicles, and formulations. For general clinicians and patients alike, navigating the various steroid classes, concentrations, and potency scales, particularly given international differences in classification, can lead to errors or under- or over-treatment.[63] Advanced topical nonsteroidal therapies help streamline regimens by providing a single, safe option appropriate for a wide range of body sites and durations of use.[2,5,6,10,13,18,21,23,25] Together, these attributes make advanced topical nonsteroidal therapies more simplified and user-friendly for long-term management. Their convenience, safety, and reduced regimen complexity can improve adherence and support sustained control of AD.

CONCLUSION

In summary, advanced topical nonsteroidal therapies represent an important evolution in the topical management of AD. These agents provide effective, steroid-sparing options that can be used head to toe across all body sites, including both thin, sensitive regions and thicker skin areas, and are appropriate for longer treatment durations; these features are central to real-world AD care. Using a structured consensus process, this panel integrated available evidence with clinical experience to clarify how these therapies can be positioned across disease severities, incorporated into combination regimens, and used to support proactive maintenance strategies. As the topical treatment landscape continues to expand, nonsteroidal therapies are likely to play an increasingly central role in improving long-term disease control and patient quality of life while minimizing the risk of adverse events associated with chronic corticosteroid use.

DISCLOSURES

AWA has served as a research investigator, scientific advisor, or speaker to AbbVie, Alumis, BMS, Galderma, Leo, UCB, J&J, Lilly, Novartis, Sun, Sanofi, Takeda, Regeneron, and Pfizer.

YN has no conflicts of interest to disclose.

CGB has served as an investigator and/or consultant for AbbVie, Almirall, Alumis, Amgen, Apogee, Arcutis, Botanix, Castle Biosciences, Connect BioPharma, Daiichi Sankyo, Dermavant, Disc Medicine, Eli Lilly, EPI Health/Novan, Galderma, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Palvella, Pfizer, Regeneron, Sanofi, South Beach Symposium, Sun Pharma, Takeda, Timber, Teladoc, Triveni, UCB, and Veradermics.

RC has served as an advisor, consultant, speaker, and/or investigator for AbbVie, Acelyrin, Alumis, Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics, Argenx, Astria Therapeutics, Avalere Health, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celldex Therapeutics, CLn Skin Care, Dermavant, Eli Lilly and Company, EMD Serono, Formation Bio, Forte Biosciences, Galderma, Genentech, GSK, Incyte, Imagene Bio Inc., Johnson & Johnson, Kenvue, Kowa Pharmaceuticals America, LEO Pharma, L'Oréal, Nektar Therapeutics, Nia Health, Novartis, Opsidio, Organon, Pfizer, RAPT, Regeneron, Sanofi, Sitryx, SUN Pharma, Takeda, TRex Bio, UCB, Zai Lab.

AAH has received funding through research grants from Pfizer, Arcutis, Dermavant/Organon, Abbvie, Amgen, Oneness, Takeda,

and Incyte; as an honoraria through Pfizer, Arcutis, Dermavant/ Organon, Abbvie, Amgen, Takeda. Incyte, Sun Pharma, Galderma, Alphyn, Ortho Dermatologics; and is on the data safety and monitoring board for Ortho Dermatologics, Sanofi Regeneron, Apogee.

LK has received funding either as an investigator, consultant, or a speaker from the following pharmaceutical companies: Abbott, Abbvie, Ablynx, Acambis, Aclaris, Allergan, Almirall, Alumis, Anaptys, Amgen, Anacor, Apogee Therapeutics, Arcutis Inc., Apollo Therapeutics, Aqua, Astellas, Asubio, Bayer, Beiersdorf Inc, Biofrontera, BMS, Bertex, Biogen-Idec, Biolife, Biopelle, Boehringer Ingleheim, Botanix Pharmaceuticals, Breckenrdige Pharma, Brickell, Cassiopea, Cellceutix, Calgene, Centocor, ChemoCentryx, Cipher, Coherus, Cipher, Coherus, Colbar, Collagenex, Combinatrix, Connectics, Coria, Dermata Therapeutics, Dermavant, Dermik, Dermira, Dow, Dusa Pharmaceuticals, Eli Lilly, Embil Pharmaceuticals, Enveda Biosciences, Exeltis, EOS, Feldan Therapeutics, Ferndale, Galderma, Genentech, Glaxo-Smith Kline, HealthPoint, Idera, Incyte Corporation, Intendia, Innovail, Isdin, Johnson and Johnson, Kymera Therapeutics, Laboratory Skin Care, 3M, Leo, L'Oreal, MC-2, Maruho, Medical International technologies, Medics, Merck, Merck Serono, Merz, NanoBio, Nektar Therapeutics, Novartis, Novan, Nucryst, Obagi, Onset Therapeutics, Organon Biosciences SRL, Ortho Dermatologics, OrthoNeutrogena, Oruka Therapeutics, PediaPharma, Pelthos, Pfizer, PharmaDerm, Promius, Puracap, QLT, Quatrix, QUinnova, Regeneron, Sagimet Biosciences, Sandoz, Sanofi, Serono, SkinMedica, Stiefel, Sun Pharma, Takeda Pharmaceuticals USA, Taro, TolerRx, Triax Pharmaceuticals, UCB, Valeant, Vellera, Warner & Chilcott, Xenoport, ZAGE, Zalicus.

JY has served as a research investigator, scientific advisor, or speaker for Arcutis, Astria, Hypothesis, Incyte, iRhythm, J&J, Leo Regeneron, Sanofi.

MGL is an employee of Mount Sinai and receives research funds from: Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Bristol Meyers Squibb,Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte,Inozyme, Johnson & Johnson, Oruka, Pfizer, Sanofi-Regeneron, and UCB, and is 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, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Galderma, Genentech, J&J, Incyte, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Meiji Seika Pharma, Moonlake, Oruka, Pfizer,Sanofi-Regeneron, Revolo, Seanergy, Strata, Sunpharma,Takeda,Trevi, and Verrica.

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doi:10.36849/JDD.9807

March 2026 228 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Expert Consensus on Advanced Topical Nonsteroidal Therapies for Chronic Hand Eczema

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ABSTRACT

Background: Chronic hand eczema (CHE) is a common, heterogeneous inflammatory skin disease associated with substantial symptom burden, impaired hand function, reduced quality of life, and work-related disability. Despite its clinical impact, evidence-based guidance for long-term, steroid-sparing topical management has been limited.

Objective: To develop expert consensus statements on the role of advanced topical nonsteroidal therapies in CHE management.

Methods: A panel of seven dermatologists with expertise in CHE conducted a structured literature review, prioritizing CHE-specific trials when available. Evidence was evaluated using the Strength of Recommendation Taxonomy (SORT). Draft statements were refined through a Delphi consensus process, with consensus predefined as ≥75% agreement.

Results: The panel reached consensus on six statements addressing advanced topical nonsteroidal therapies in CHE. These agents were recognized as important steroid-sparing options appropriate for long-term use. Delgocitinib cream is currently the only topical therapy with CHE-specific regulatory approval and is considered an appropriate first-line advanced topical treatment. Clinical trial data show that advanced topical nonsteroidal therapies provide rapid and sustained improvements in erythema, scaling, fissuring, pruritus, and pain. Delgocitinib demonstrated sustained improvements in patient-reported outcomes and superior health-related quality-of-life benefits compared with oral alitretinoin in severe CHE. Treatment has also been associated with improved work productivity and daily functioning. These therapies have favorable safety profiles, with adverse events largely limited to local reactions, minimal systemic exposure, and no requirement for routine laboratory monitoring. Other topical nonsteroidal agents may have a role in selected patients, although CHE-specific data remain limited.

Conclusion: This consensus provides practical guidance supporting individualized, steroid-sparing CHE management while identifying areas for future research.

J Drugs Dermatol. 2026;25(3):228-233. doi:10.36849/JDD.9807

INTRODUCTION

Chronic hand eczema (CHE) is a common, heterogeneous inflammatory condition affecting the hands and wrists. Etiologic and morphologic patterns, such as irritant, allergic, atopic, hyperkeratotic, vesicular, and mixed presentations, are often described; however, these features frequently overlap in clinical practice and are generally considered within the broader diagnosis of CHE.[1,2] The European Society of Contact Dermatitis defines CHE as hand eczema lasting at least three months or recurring two or more times within a year.[3-5] As a result, while descriptive patterns may be helpful for clinical context, management is often guided by the overall diagnosis of CHE rather than strict subtyping. The scope of this work is limited to CHE as defined by these criteria and does not include pediatric disease.

CHE has substantial personal and societal impact. Both US Department of Labor and European occupational health data identify hand dermatitis as a major contributor to work absenteeism and productivity loss.[6-8] Despite this burden, only one topical therapy is currently approved for CHE, leaving clinicians with limited options for a condition that often requires long-term management (Table 1).[9] Although several advanced topical nonsteroidal agents are used in practice, evidence specific to CHE remains limited, and clinicians often extrapolate from studies of atopic dermatitis or contact dermatitis. Small studies suggest potential benefit but highlight the need for clearer guidance.[10]

TABLE 1.

FDA-Approved and Off-Label Use of Nonsteroidal Agents for Chronic Hand Eczema

Medication	Mechanism of Action	FDA Approval Status	Formulation Strength
Delgocitinib	Pan JAK inhibitor: Inhibits JAK1, JAK2, JAK3, and TYK2 enzymes	Yes	Cream, 2%, Applied twice daily
Ruxolitinib	Inhibits JAK1 and JAK2	No	Cream, 1.5%, Applied twice daily*
Tapinarof	Aryl-hydrocarbon receptor agonist	No	Cream, 1%, Applied once daily*
Roflumilast	Phosphodiesterase-4 (PDE-4) inhibitor	No	Cream, 0.15% or 0.05%, Applied once daily*
Crisaborole	Phosphodiesterase-4 (PDE-4) inhibitor	No	Ointment, 2%, Applied twice daily*
Pimecrolimus	Calcineurin inhibitor; blocks T-cell activation by binding to FKBP-12	No	Cream, 1%, Applied twice daily*
Tacrolimus	Calcineurin inhibitor; blocks T-cell activation by binding to FK506 binding protein	No	Ointment, 0.03% and 0.1%, Applied twice daily*

Abbreviations: *Used off-label for chronic hand eczema; FDA, Food and Drug Administration; JAK, janus kinase inhibitor; TYK2, tyrosine kinase 2

To support clinical decision-making, an expert panel convened to develop consensus statements on the use of topical nonsteroidal therapies for CHE. This manuscript summarizes the panel's process and provides evidence-informed recommendations to guide practical management of CHE.

MATERIALS AND METHODS

Consensus Development Process

An expert panel of seven dermatologists with clinical and research expertise in CHE, contact dermatitis, atopic dermatitis, and topical therapeutics was convened to develop evidence-informed consensus statements on the use of advanced topical nonsteroidal therapies for CHE (AWA, CGB, RC, AAH, LK, JY, MGL). Panelists were selected based on clinical and research experience managing CHE across diverse clinical settings.

The panel used the Strength of Recommendation Taxonomy (SORT) framework to grade available evidence and to guide the development of recommendations.[11] Evidence was categorized by the quality and consistency of data supporting each therapy (by YN), with emphasis on CHE-specific clinical trials when available. We conducted a structured Delphi consensus process beginning following the aforementioned literature review, after which each panelist independently appraised and rated all publications contributing to the evidence base. These individual assessments informed the development of draft statements, which were subsequently evaluated by the panel using standardized Delphi rating formats. Consensus was defined a priori as ≥75% agreement among panel members. Statements meeting this threshold were advanced to the final recommendations, ensuring that each reflects both systematic evidence appraisal and expert convergence.

RESULTS

The expert panel reached consensus on six key statements addressing the role of advanced topical nonsteroidal therapies in CHE. These statements summarize the available evidence and provide practical guidance for clinicians managing this heterogeneous and burdensome condition (Table 2).

TABLE 2.

Consensus Statements for Chronic Hand Eczema

Statement	Strength of Recommendation	Consensus Vote
Statement 1: Delgocitinib is the only approved topical treatment for chronic hand eczema and an appropriate first-line advanced therapy.	A	7/7
Statement 2: Advanced topical nonsteroidal therapies provide rapid and sustained improvement in signs and symptoms of chronic hand eczema, including skin pain and pruritus.	A	7/7
Statement 3: Advanced topical nonsteroidal therapies improve quality of life in patients with chronic hand eczema.	A	7/7
Statement 4: Advanced topical nonsteroidal therapies for chronic hand eczema improve productivity and activities of daily living and decrease work-related disability.	C	7/7
Statement 5: Among approved therapies, delgocitinib demonstrates superior efficacy and tolerability compared to oral alitretinoin in chronic hand eczema.	A	7/7
Statement 6: Advanced topical nonsteroidal therapies for chronic hand eczema are safe, well-tolerated, and do not require laboratory workup.	A	7/7

Statement 1: Delgocitinib is the only approved topical treatment for chronic hand eczema and an appropriate first-line advanced therapy.

Delgocitinib represents the first and only topical therapy approved specifically for CHE and addresses a long-standing therapeutic gap for this heterogeneous and often treatment-resistant condition.[9,12] CHE encompasses multiple subtypes, and delgocitinib has demonstrated efficacy across these variants.[12-15] In clinical trials, twice-daily delgocitinib cream provided significant reductions in signs and symptoms such as erythema, scaling, fissuring, and pruritus, with meaningful improvement typically observed within several weeks.[16] The nonsteroidal profile also makes it a useful option for long-term disease control without the risks associated with chronic topical corticosteroid (TCS) use, including skin atrophy, tachyphylaxis, and recurrent steroid cycling.[17,18] Prolonged TCS exposure may also adversely affect skin barrier integrity, which can be particularly relevant in CHE.

Although delgocitinib is the only topical agent with a CHE-specific regulatory approval, its formulation was specifically developed for use on the hands, with the exclusion of several common excipients that may be problematic in this setting. Other topical nonsteroidal therapies may have a role in management when CHE overlaps with atopic dermatitis (AD) or when patients carry dual diagnoses. Ruxolitinib cream, approved for atopic dermatitis and studied in certain forms of chronic hand eczema, may be appropriate in carefully selected patients with AD-associated hand disease, as clinical studies have demonstrated antipruritic effects and improvements in inflammatory signs despite the absence of CHE-specific regulatory approval.[19,20] Tapinarof, an aryl hydrocarbon receptor agonist, approved for AD and psoriasis, offers anti-inflammatory and barrier-supportive effects that could theoretically benefit hand involvement, though CHE-specific data are lacking.[21,22] Similarly, topical roflumilast, a highly potent PDE-4 inhibitor approved for AD, provides strong anti-inflammatory activity and favorable tolerability on sensitive skin sites, but evidence specific to CHE remains limited.[23-25] Crisaborole, a PDE-4 inhibitor, has limited but supportive real-world evidence in atopic hand dermatitis and may be considered for patients whose hand disease reflects atopic mechanisms.[10]

Beyond topical agents, emerging data for systemic biologics, including dupilumab and tralokinumab, demonstrate improvement in hand dermatitis among patients with atopic dermatitis.[26,27] Collectively, delgocitinib remains the only evidence-based, CHE-specific topical therapy and serves as an appropriate first-line advanced option. Its nonsteroidal, anti-inflammatory profile offers a steroid-sparing strategy that reduces the need for chronic corticosteroid cycling and supports long-term disease control across diverse CHE subtypes.[14] These therapeutic benefits are driven by delgocitinib's pan-JAK inhibition, which broadly modulates inflammatory signaling implicated in CHE.

Statement 2: Advanced topical nonsteroidal therapies provide rapid and sustained improvement in signs and symptoms of chronic hand eczema, including skin pain and pruritus.

Clinical trials of delgocitinib provide the strongest evidence that advanced topical nonsteroidal therapies offer both rapid and durable improvement across the spectrum of CHE symptoms. In randomized studies, twice-daily delgocitinib led to significant reductions in erythema, scaling, fissuring, skin pain, and pruritus, with meaningful symptom relief emerging as early as week 4.[12,16] Improvements were captured using CHE-specific instruments such as the Hand Eczema Severity Index (HECSI), the Physician's Global Assessment (PGA), and the Hand Eczema Symptom Diary (HESD), which measures patient-reported itch, burning, stinging, skin tightness, and pain. These multidimensional effects underscore delgocitinib's broad impact on both clinical signs and daily symptom burden. Long-term extension studies show that clinical gains achieved with delgocitinib can be maintained for up to one year, supporting its role as a sustained-control therapy for CHE.[14]

Other nonsteroidal agents may ameliorate symptoms when CHE presents in the context of atopic dermatitis. Ruxolitinib cream, although not approved for CHE, has demonstrated rapid antipruritic effects within weeks in certain types of CHE, underscoring the relevance of JAK-mediated itch reduction for select patients.[19] Tapinarof and roflumilast have shown improvements in itch, erythema, and skin discomfort in AD or psoriasis, suggesting they may help address inflammatory features of CHE, even though CHE-specific studies are not yet available.[22,23,25,28]

Taken together, these data highlight a broader therapeutic landscape in which delgocitinib provides the most robust, CHE-specific evidence, while other advanced topical nonsteroidal therapies may supplement management in patients whose hand eczema is driven by, or coexists with, other inflammatory conditions. These options may help address symptom domains such as itch and discomfort that contribute to functional impairment, complementing the central role of delgocitinib in CHE care.

Statement 3: Advanced topical nonsteroidal therapies improve quality of life in patients with chronic hand eczema.

Delgocitinib cream 20 mg/g, a topical pan-JAK inhibitor, significantly improves quality of life in patients with CHE through reductions in disease severity, itch, and pain. In the pivotal DELTA 1 and DELTA 2 trials, delgocitinib demonstrated superior efficacy versus vehicle in patient-reported outcomes, including improvements in the Dermatology Life Quality Index

(DLQI), itch, and skin pain in adults with moderate to severe CHE.[12,16] These quality-of-life benefits were sustained with long-term as-needed treatment in the open-label DELTA 3 extension study.[14]

The DELTA FORCE head-to-head trial further demonstrated that delgocitinib cream showed superior health-related quality of life improvements compared with oral alitretinoin in patients with severe CHE over 24 weeks.[13] This represents a meaningful advance for a patient population with substantial disease burden affecting occupational capabilities and social interactions. As a non-steroidal topical option, delgocitinib addresses the unmet need for effective disease control without the safety concerns of long-term TCS or systemic therapies. The favorable safety profile, with low systemic exposure and good local tolerability, further contributes to its potential to improve overall patient well-being.[15,29] Evidence for other topical nonsteroidal therapies in improving quality of life for CHE is limited at this time.

Statement 4: Advanced topical nonsteroidal therapies for chronic hand eczema improve productivity and activities of daily living and decrease work-related disability.

Delgocitinib cream 20 mg/g demonstrates substantial improvements in work productivity and activities of daily living in patients with CHE, with evidence from the DELTA trials showing clinically meaningful reductions in disease burden that directly impact occupational and functional capacity.[12,13] In the pivotal DELTA 1 and DELTA 2 trials, delgocitinib-treated patients experienced significant improvements in health-related quality of life measures, including the Dermatology Life Quality Index (DLQI), which captures work and daily activity limitations.[12] The health-related quality of life improvements with delgocitinib, including work limitations, was superior compared to oral alitretinoin in patients with severe CHE.[13] Early symptom relief beginning at week 1 for itch and pain reduction suggests rapid restoration of hand function.[12,16] CHE affects up to 10% of the general population and is associated with significant impaired hand function and reduced quality of life, making these functional improvements particularly meaningful for work-related disability.[29]

Evidence for other topical nonsteroidal treatments improving productivity and daily activities in CHE is limited. Tacrolimus 0.1% ointment, recommended as second-line therapy, has shown improvements in patient-reported symptoms in network meta-analyses, though specific data on work productivity outcomes in hand eczema are sparse.[30,31] The broader quality of life benefits observed with delgocitinib position it as a corticosteroid-sparing alternative that addresses the substantial occupational burden of this condition.

Statement 5: Among approved therapies, delgocitinib demonstrates superior efficacy and tolerability compared to oral alitretinoin in chronic hand eczema.

Delgocitinib cream 20 mg/g has been shown to outperform oral alitretinoin in adults with severe CHE, based on findings from the DELTA FORCE head-to-head trial.[13] In this randomized, assessor-masked phase 3 study, patients treated with delgocitinib achieved greater reductions in Hand Eczema Severity Index (HECSI) scores at week 12—the primary endpoint—and again at week 24. These benefits extended beyond HECSI improvement: delgocitinib was associated with higher rates of IGA-CHE treatment success and better patient-reported outcomes for itch, pain, and overall quality of life. Treatment differences emerged as early as week 1 and were maintained throughout the 24-week study period.

Safety and tolerability results also favored delgocitinib. Patients using the topical therapy experienced fewer adverse events, fewer serious events, and fewer treatment discontinuations compared with those receiving oral alitretinoin.[13] As anticipated from its known profile, alitretinoin was associated with metabolic changes—such as elevated cholesterol and triglycerides—and a higher frequency of treatment cessation due to side effects, lack of efficacy, or patient preference. Gastrointestinal symptoms, including nausea, were also reported with alitretinoin, an issue entirely avoided with topical delgocitinib. Because delgocitinib is applied to a limited skin area, systemic absorption is minimal, eliminating the systemic exposure and safety concerns associated with oral retinoids and systemic JAK inhibition. This reduced burden is particularly relevant for patients who cannot tolerate oral retinoids or who have contraindications, including women of childbearing potential.

Statement 6: Advanced topical nonsteroidal therapies for chronic hand eczema are safe, well-tolerated, and do not require laboratory workup.

Advanced topical nonsteroidal therapies have demonstrated strong safety and tolerability in the management of CHE, offering an important advantage over systemic options that require laboratory monitoring. Delgocitinib cream 20 mg/g, the only topical therapy approved specifically for CHE, has consistently shown a favorable safety profile with low rates of local reactions and negligible systemic adverse effects.[12,14] Unlike all other JAK inhibitors to date, which carry boxed warnings and require periodic laboratory assessment, topical delgocitinib does not trigger the systemic safety concerns associated with JAK inhibition due to its minimal systemic absorption. Pharmacokinetic assessments confirm that delgocitinib plasma levels remain well below thresholds associated with systemic JAK activity, even under maximal-use conditions.[32,33]

The delgocitinib maximal-use study, which evaluated application to large body surface areas under real-world dosing intensity, further demonstrated the absence of clinically meaningful systemic exposure.[34] No laboratory abnormalities or systemic safety signals were observed, reinforcing the suitability of delgocitinib for chronic or recurrent use without the need for

routine bloodwork. This stands in contrast to oral agents used historically for severe hand eczema, such as alitretinoin, which require laboratory monitoring for lipid elevations and carry additional safety considerations including teratogenicity and mucocutaneous side effects.

Other advanced topical nonsteroidal agents, such as roflumilast, tapinarof, and crisaborole, also offer favorable safety profiles, with adverse events largely limited to transient application-site reactions and no systemic monitoring requirements.[35-38] Together, these therapies provide safe, well-tolerated options for long-term management of CHE and reduce reliance on chronic topical corticosteroids or systemic therapies that carry greater safety burdens.

CONCLUSION

In summary, CHE is a highly burdensome, heterogeneous condition for which treatment options have historically been limited, particularly for patients requiring long-term, steroid-sparing control. Based on a structured evidence review and Delphi process, this expert panel concludes that delgocitinib cream is an appropriate first-line advanced topical nonsteroidal therapy for CHE, offering rapid and sustained improvement in signs, symptoms, quality of life, and work productivity with a favorable safety profile and no need for laboratory monitoring. While many patients experience early clinical improvement, others may require consistent application over longer treatment durations to achieve optimal response, highlighting the importance of adherence and appropriate expectations in real-world management. Other advanced topical nonsteroidals may have a role in selected patients, particularly when CHE overlaps with atopic dermatitis or other inflammatory dermatoses; for example, ruxolitinib cream has demonstrated clinical benefit in certain forms of CHE but is not currently approved for this indication, while disease-specific data for other agents remain limited. These consensus statements provide a practical framework to help clinicians individualize therapy, minimize chronic corticosteroid exposure, and address the substantial functional and psychosocial impact of CHE, while highlighting key gaps that should be prioritized in future clinical trials and real-world studies.

DISCLOSURES

AWA has served as a research investigator, scientific advisor, or speaker to AbbVie, Alumis, BMS, Galderma, Leo, UCB, J&J, Lilly, Novartis, Sun, Sanofi, Takeda, Regeneron, and Pfizer.

YN has no conflicts of interest to disclose.

CGB has served as an investigator and/or consultant for AbbVie, Almirall, Alumis, Amgen, Apogee, Arcutis, Botanix, Castle Biosciences, Connect BioPharma, Daiichi Sankyo, Dermavant, Disc Medicine, Eli Lilly, EPI Health/Novan, Galderma, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Palvella, Pfizer, Regeneron, Sanofi, South Beach Symposium, Sun Pharma, Takeda, Timber, Teladoc, Triveni, UCB, and Veradermics.

RC has served as an advisor, consultant, speaker, and/or investigator for AbbVie, Acelyrin, Alumis, Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics, Argenx, Astria Therapeutics, Avalere Health, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celldex Therapeutics, CLn Skin Care, Dermavant, Eli Lilly and Company, EMD Serono, Formation Bio, Forte Biosciences, Galderma, Genentech, GSK, Incyte, Imagene Bio Inc., Johnson & Johnson, Kenvue, Kowa Pharmaceuticals America, LEO Pharma, L'Oréal, Nektar Therapeutics, Nia Health, Novartis, Opsidio, Organon, Pfizer, RAPT, Regeneron, Sanofi, Sitryx, SUN Pharma, Takeda, TRex Bio, UCB, Zai Lab.

AAH has received funding through research grants from Pfizer, Arcutis, Dermavant/Organon, Abbvie, Amgen, Oneness, Takeda, and Incyte; as an honoraria through Pfizer, Arcutis, Dermavant/Organon, Abbvie, Amgen, Takeda Incyte, Sun Pharma, Galderma, Alphyn, Ortho Dermatologics; and is on the data safety and monitoring board for Ortho Dermatologics, Sanofi Regeneron, Apogee.

LK has received funding either as an investigator, consultant, or a speaker from the following pharmaceutical companies: Abott, Abbvie, Ablynx, Acambis, Aclaris, Allergan, Almirall, Alumis, Anaptys, Amgen, Anacor, Apogee Therapeutics, Arcutis Inc., Apollo Therapeutics, Aqua, Astellas, Asubio, Bayer, Beiersdorf Inc, Biofrontera, BMS, Bertex, Biogen-Idec, Biolife, Biopelle, Boehringer-Ingleheim, Botanix Pharmaceuticals, Breckenrdige Pharma, Brickell, Cassiopea, Cellceutix, Calgene, Centocor, ChemoCentryx, Cipher, Coherus, Cipher, Coherus, Colbar, Collagenex, Combinatrix, Connectics, Coria, Dermata Therapeutics, Dermavant, Dermik, Dermira, Dow, Dusa Pharmaceuticals, Eli Lily, Embil Pharmaceuticals, Enveda Biosciences, Exeltis, EOS, Feldan Therapeutics, Ferndale, Galderma, Genentech, Glaxo-Smith Kline, HealthPoint, Idera, Incyte Corporation, Intendia, Innovail, Isdin, Johnson and Johnson, Kymera Therapeutics, Laboratory Skin Care, 3M, Leo, L'Oreal, MC-2, Maruho, Medical International technologies, Medics, Merck, Merck Serono, Merz, NanoBio, Nektar Therapeutics, Novartis, Novan, Nucryst, Obagi, Onset Therapeutics, Organon Biosciences SRL, Ortho Dermatologics, OrthoNeutrogena, Oruka Therapeutics, PediaPharma, Pelthos, Pfizer, PharmaDerm, Promius, Puracap, QLT, Quatrix, QUinnova, Regeneron, Sagimet Biosciences, Sandoz, Sanofi, Serono, SkinMedica, Stiefel, Sun Pharma, Takeda Pharmaceuticals USA, Taro, TolerRx, Triax Pharmaceuticals, UCB, Valeant, Vellera, Warner & Chilcott, Xenoport, ZAGE, Zalicus.

JY has served as a research investigator, scientific advisor, or speaker for Arcutis, Astria, Hypothesis, Incyte, iRhythm, J&J, Leo Regeneron, Sanofi.

MGL is an employee of Mount Sinai and receives research funds from: Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Bristol Meyers Squibb, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Johnson & Johnson, Oruka, Pfizer, Sanofi-Regeneron, and UCB, and is 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, Evommune, Inc., Facilitation of International Dermatology Education,Forte biosciences, Galderma, Genentech, J&J, Incyte, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Meiji Seika Pharma, Moonlake, Oruka, Pfizer, Sanofi-Regeneron, Revolo, Seanergy, Strata, Sunpharma,Takeda,Trevi, and Verrica.

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doi:10.36849/JDD.9474R1

March 2026 234 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Antiviral Treatment of Herpes Simplex Virus Decreases the Risk of Alzheimer's Disease and Dementia

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ABSTRACT

Background: Alzheimer's disease (AD) and dementia create major global health and economic burdens. Herpes simplex virus (HSV) infects over 3 billion people, and chronic infection is increasingly linked to neurodegeneration.

Objectives: To evaluate whether antiviral therapy for oral, mucocutaneous, or anogenital HSV lowers the subsequent risk of AD and dementia.

Methods: A retrospective cohort study with propensity-score matching was performed in the TriNetX Research Network. On 24 May 2024, 615,324 individuals with HSV were identified; those with prior AD, intracranial injury, or cerebral infarction were excluded. Matching balanced age, sex, race, body-mass index, smoking, diabetes, and hypertension between antiviral-treated and untreated groups. Therapies included acyclovir, valacyclovir, penciclovir, ganciclovir, valganciclovir, and famciclovir. Incidences of AD and dementia were identified by ICD-10 codes, and relative risks (RR) with 95% confidence intervals (CI) were calculated.

Results: After matching, 231,277 patients per cohort (mean age 36.8 y; 67.7% female) were analyzed. Antiviral treatment for oral/mucocutaneous HSV significantly reduced the risk of AD (RR 0.87; 95% CI 0.73-0.92) and dementia (RR 0.83; 95% CI 0.77-0.90). No significant association was observed for anogenital HSV.

Conclusions: Antiviral therapy for oral or mucocutaneous HSV was associated with a 13% to 17% reduction in risk for AD and dementia. These findings suggest that early antiviral management of HSV infections may represent a feasible preventive strategy against neurodegenerative disease, meriting prospective confirmation.

J Drugs Dermatol. 2026;25(3):234-239. doi:10.36849/JDD.9474R1

INTRODUCTION

Herpes simplex virus (HSV), responsible for oral and genital herpes, impacts over 3 billion people worldwide.[1] HSV-1 typically causes oral herpes, while HSV-2 usually leads to genital herpes, though either virus can infect both anatomical sites.[1-5] HSV lesions are often self-limiting, and thus antiviral treatment is not routinely prescribed for all cases.[6] Furthermore, HSV may not always cause apparent mucocutaneous lesions and may appear to be dormant in the trigeminal sensory ganglion.[6] HSV-2 is associated with a 3-fold increased risk of contracting human immunodeficiency virus (HIV) infection.[7] About one-third of Americans have recurrent labial herpes (1-6 outbreaks/year).[8,9] Under current guidelines, patients experiencing severe and frequent HSV outbreaks (>6 per year) may receive antiviral therapy for treatment and prophylaxis.[9]

Alzheimer's disease (AD) is a progressive debilitating neurologic disorder characterized by impaired behavior and cognition.[10] In 2023, the prevalence of AD was 6.7 million in the US and is projected to increase to 13.8 million by 2060.[11] Known risk factors for AD include cardiovascular disease, obesity, cigarette smoking, and diabetes mellitus.[12] Over $345 billion USD was spent on AD and dementia treatment in 2022, and this cost is estimated to increase to over $1 trillion by 2050.[11,13] As of 2024, the US federal government is investing $3.8 billion USD on AD and dementia research, highlighting the urgent need for new insights and interventions.[14]

The risk of developing AD increases by 1.5 to 3.5 times in individuals with a history of HSV;[6] notably, prior studies observed lower AD prevalence in HSV-infected patients treated with antivirals vs untreated cohorts.[15-17] Supporting

this broader viral hypothesis, a recent study published in *Nature* demonstrated a 20% relative reduction in dementia diagnoses following herpes zoster vaccination over a 7-year follow-up period.[18] Although that investigation focused on varicella-zoster virus (VZV), its shared neurotropism and reactivation profile with HSV supports antiviral suppression as a dementia-mitigating strategy.[18] These findings support the central premise of our study: that antiviral strategies targeting latent viral infections may significantly reduce the risk of neurodegenerative diseases, including dementia and AD. Herein, we aim to investigate whether antiviral treatment for oral, mucocutaneous, and anogenital HSV infections is associated with a decreased risk of developing AD and other types of dementia.

MATERIALS AND METHODS

Data were collected on May 24, 2024 from the State University of New York (SUNY) Downstate TriNetX Research Network, a longitudinal health database containing electronic medical records from approximately 124 million patients across 86 healthcare organizations.

This retrospective cohort study investigated whether antiviral therapy for oral, mucocutaneous, and anogenital HSV infections is associated with reduced risk of AD or dementia compared with untreated patients. In this study, ICD-10 code B-00, Herpesviral [herpes simplex] infections, is classified as representing oral and mucocutaneous HSV (OMC-HSV) infections, given that these are the most impacted anatomic sites.[19] ICD-10 code A-60,

TABLE 1.

Baseline Characteristics of Oral and Mucocutaneous Herpes Simplex Virus Study Participants Before and After Propensity-Score Matching

	Before Propensity-Score Matching		After Propensity-Score Matching	
	HSV/AV, n (%)	HSV/No AV, n (%)	HSV/AV, n (%)	HSV/No AV, n (%)
Total Patients	586,572	251,147	231,539	231,539
Age at Index, mean (SD), y	42.1 ± 18.7	34.0 ± 22.7	37.4 ± 20.3	36.2 ± 22.1
Gender				
Male	152,621 (26.0%)	80,424 (32.0%)	69,739 (30.1%)	68,260 (29.5%)
Female	414,390 (70.6%)	164,321 (65.4%)	156,234 (67.5%)	156,885 (67.8%)
Unknown	19,561 (3.3%)	6,402 (2.5%)	5,566 (2.4%)	6,394 (2.8%)
Race				
White	382,444 (65.2%)	134,648 (53.6%)	131,103 (56.6%)	132,969 (57.4%)
Black or African American	80,455 (13.7%)	40,770 (16.2%)	36,431 (15.7%)	37,509 (16.2%)
Asian	16,441 (2.8%)	7,963 (3.2%)	7,351 (3.2%)	7,592 (3.3%)
American Indian or Alaska Native	1,730 (0.3%)	655 (0.3%)	656 (0.3%)	655 (0.3%)
Native Hawaiian or Other Pacific Islander	1,381 (0.2%)	714 (0.3%)	680 (0.3%)	714 (0.3%)
Other Race	25,709 (4.4%)	13,118 (5.2%)	11,796 (5.1%)	12,355 (5.3%)
Unknown Race	78,412 (13.4%)	53,279 (20.8%)	43,522 (18.8%)	39,509 (17.1%)
Comorbidities				
Hypertensive Diseases	127,835 (21.8%)	32,738 (13.0%)	34,205 (14.8%)	19,522 (8.4%)
Body Mass Index	86,739 (14.8%)	19,995 (8.0%)	19,522 (8.4%)	19,979 (8.6%)
Diabetes Mellitus	47,640 (8.1%)	13,292 (5.3%)	13,731 (5.9%)	13,207 (5.7%)
Tobacco Use	13,814 (2.4%)	3,551 (1.4%)	3,491 (1.5%)	3,551 (1.5%)

AV, antiviral; HSV, herpes simplex virus.

TABLE 2.

Risk of Developing Forms of Dementia for Oral and Mucocutaneous Herpes Simplex Virus Patients Treated With Antiviral Therapy After Propensity-Score Matching

	Alzheimer's Disease		Vascular Dementia		Dementia in Other Diseases		Unspecified Dementia	
	AV	No-AV	AV	No-AV	AV	No-AV	AV	No-AV
# of Outcomes	509	623	288	304	763	799	1145	1379
Risk %	0.22%	0.269%	0.124%	0.131%	0.33%	0.346%	0.496%	0.598%
Risk Difference % (95% CI)	-0.049%* (-0.078% to -0.021%)		-0.007% (-0.028% to 0.014%)		-0.016% (-0.049% to 0.018%)		-0.102%* (-0.144% to -0.059%)	
Risk Ratio (95% CI)	0.871* (0.727 to 0.918)		0.947 (0.806 to 1.113)		0.955 (0.865 to 1.054)		0.83* (0.767 to 0.897)	

*Indicates (P<0.05).
AV, antiviral.

TABLE 3.

Risk of Developing Forms of Dementia for Anogenital Herpes Simplex Virus Patients Treated With Antiviral Therapy After Propensity-Score Matching

	Alzheimer's Disease		Vascular Dementia		Dementia in Other Diseases		Unspecified Dementia	
	AV	No-AV	AV	No-AV	AV	No-AV	AV	No-AV
# of Outcomes	90	95	47	50	133	130	199	231
Risk %	0.118%	0.124%	0.062%	0.065%	0.174%	0.17%	0.261%	0.303%
Risk Difference % (95% CI)	-0.007% (-0.041% to 0.028%)		-0.004% (-0.029% to 0.021%)		0.004% (-0.038% to 0.046%)		-0.042% (-0.095% to 0.011%)	
Risk Ratio (95% CI)	0.947 (0.71 to 1.263)		0.94 (0.631 to 1.399)		1.023 (0.804 to 1.303)		0.861 (0.713 to 1.041)	

AV, antiviral.

Anogenital herpesviral [herpes simplex] infections, is classified as anogenital HSV infections. Patients diagnosed with AD, ICD-10 code G-30, prior to being diagnosed with an HSV infection were excluded to isolate for the incidence of AD and other forms of dementia after being infected with oral, mucocutaneous, or anogenital HSV. Patients who had an intracranial injury or cerebral infarction at any point in their lives were excluded from this study, as these are independent diagnoses associated with AD.

Antiviral treatments included acyclovir, valacyclovir, penciclovir, ganciclovir, valganciclovir, and famciclovir. Propensity-based cohort matching was performed based on the following covariates: age at index, current age, sex, race, ethnicity, body mass index (BMI), tobacco use, diabetes mellitus, and hypertensive diseases, as they are all risk factors for AD and dementia (Table 1).[10] Relative risk (RR) and 95% confidence intervals (CIs) were calculated comparing antiviral-treated vs untreated patients with oral, mucocutaneous, or anogenital HSV infections. AD, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia were analyzed independently to determine the associations of oral, mucocutaneous, or anogenital HSV infections, treated and untreated, with these diseases. Unspecified dementia refers to dementia that lacks a definitive diagnosis or identifiable cause, hereafter referred to as "dementia."[20]

Outcomes with significant associations were further analyzed to determine the association with specific OMC-HSV infections using subcategories of ICD-10 B-00. Although herpesviral meningitis, encephalitis, and disseminated herpesviral disease are not classified as mucocutaneous infections, they have been categorized within this group in our study due to their frequent origin from primary mucocutaneous HSV infections or reactivation of a latent infection that followed an initial mucocutaneous infection.[19,21] All statistics were performed on the TriNetX statistical program. Significance was obtained using the Pearson X^2 test for independence. Because this study uses deidentified patient records, it was deemed exempt from Institutional Review Board (IRB) approval by SUNY Downstate IRB.

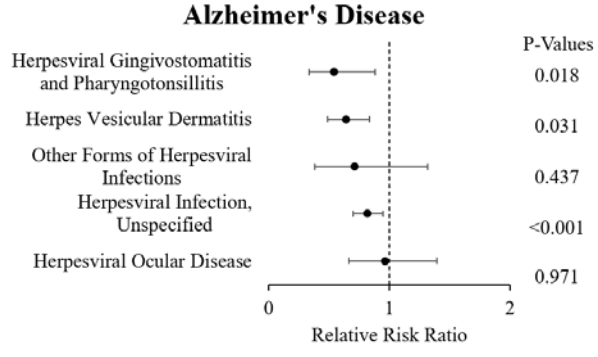
RESULTS

Oral and Mucocutaneous Herpes Simplex Virus Infections

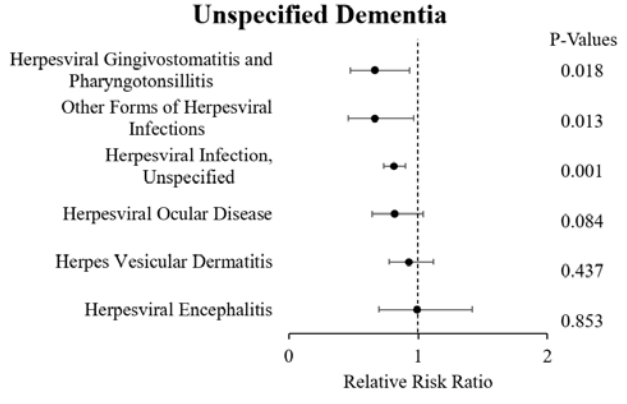
A total of 595,539 patients with a history of an oral or mucocutaneous HSV infection and any antiviral treatment were identified, while 267,956 patients had an oral or mucocutaneous HSV infection without antiviral treatment. Baseline characteristics, including age at index, sex, race, and comorbidities, are listed for each group before and after propensity-score matching in Table 1. After propensity-score matching, 231,277 patients remained in both cohorts.

FIGURE 1. Risk of developing (A) Alzheimer's disease or (B) unspecified dementia after antiviral treatment based on the subcategories of herpesviral (herpes simplex) infections, ICD-10 Codes B00.0 to B00.9. Subcategories with 10 or fewer outcomes are not shown as TriNetX only explores cohorts of 10 patients or more.

(A)



(B)



Patients who were treated with antiviral therapy were associated with a significantly decreased risk of being diagnosed with AD (RR, 0.871; 95% CI, 0.727-0.918; *P*<0.05) and dementia (RR, 0.83; 95% CI, 0.767-0.897; *P*<0.05), compared with patients not treated with antiviral therapy. Patients treated with antivirals were associated with a slightly decreased risk of developing vascular dementia (RR, 0.947; 95% CI, 0.806-1.113; *P*>0.05) and dementia in other diseases classified elsewhere (RR, 0.955; 95% CI, 0.865-1.054; *P*>0.05), but the results were not significant (Table 2).

Patients diagnosed with herpes vesicular dermatitis (RR, 0.639; 95% CI, 0.488-0.836; *P*<0.05), herpesviral gingivostomatitis and pharyngotonsillitis (RR, 0.543; 95% CI, 0.334-0.884; *P*<0.05), and herpesviral infection (RR, 0.815; 95% CI, 0.701-0.948; *P*<0.05) were all associated with a significantly decreased risk of developing AD when treated with antiviral therapy (Figure 1A). Patients diagnosed with herpesviral gingivostomatitis and pharyngotonsillitis (RR, 0.666; 95% CI, 0.474-0.933; *P*<0.05), other forms of herpesviral infections (RR, 0.666; 95% CI, 0.459-0.967; *P*<0.05), and herpesviral infection (RR, 0.814; 95% CI, 0.736-0.901; *P*<0.05) were all associated with a significantly decreased risk of developing dementia when treated with antiviral therapy (Figure 1B). TriNetX is only able to explore cohorts greater than 10 patients, thus some of the subcategories of HSV-1 could not be analyzed.

Anogenital Herpes Simplex Virus Infections

A total of 207,408 patients with a history of an anogenital HSV infection and any antiviral treatment were identified, while 81,613 patients had an anogenital HSV infection without antiviral treatment. After propensity-score matching using the same covariates as above, 76,385 patients remained in both cohorts. Patients treated with antiviral therapy did not have a decreased risk of being diagnosed with AD, vascular dementia, dementia in other diseases classified elsewhere, or dementia (Table 3).

DISCUSSION

Our study demonstrates a significant association between antiviral treatment for HSV and a reduced risk of developing Alzheimer's disease and dementia. Given the global burden of HSV infection – impacting over three billion individuals – and the growing evidence of its role in neurodegenerative disease, this work has meaningful implications for clinical practice and public health.[1]

Patients with OMC-HSV treated with antivirals had significantly lower risks of developing Alzheimer's disease (AD) and dementia. The greatest reductions in risk for AD were observed with ICD-B00.2 (herpesviral gingivostomatitis and pharyngotonsillitis), which also showed the highest risk reduction for dementia, along with ICD-B00.8 (other herpesviral infections). No significant differences were observed for vascular dementia or dementia classified elsewhere. A nationwide Swedish registry study similarly found reduced dementia risk among antiviral-treated HSV patients, though it did not stratify results by HSV infection site.[15]

In support of these findings, a 2025 *Nature* study found that herpes zoster vaccination reduced incident dementia by 20% over 7 years.[18] These data strengthen the hypothesis that reactivation of neurotropic herpesviruses contributes to neurodegeneration, and that viral suppression – whether by vaccination or antiviral therapy – can modify disease risk.[18] Although that investigation focused on varicella-zoster virus, its protective effect reinforces the broader link between herpesvirus control and lower dementia incidence, lending credence to our

HSV findings. Leveraging a larger, more diverse dataset, our analysis clarifies the role of OMC-HSV in AD and dementia; dermatologists are therefore uniquely positioned to deploy antiviral therapy as a pragmatic public health measure, playing a crucial role in addressing this expanding public-health crisis.

The underlying mechanism involving the associated reduction in relative risk of AD and other forms of dementia with antiviral therapy is currently unknown.[22] Our hypothesis is that HSV infection and flares are associated with neuronal inflammation that results in repeated brain injury, causing AD. Others have similarly theorized that HSV-1 leads to an increased risk of AD due to mechanisms involving HSV-1 induced neuronal DNA damage, alterations of cellular homeostasis pathways, promotion of neuroinflammation, and subsequent induction of amyloid-β plaque formation, the key pathological feature in AD.[23] We postulate that there may be a benefit to including HSV-1 and HSV-2 antibodies in routine bloodwork testing to determine HSV infection and titers to monitor disease status. It is important to note that studies have investigated the association of anti-HSV IgG and anti-HSV IgM antibodies with AD and dementia with mixed results. One meta-analysis concluded anti-HSV IgG was not associated with dementia, but recent infection with or reactivation of HSV, as indicated by anti-HSV IgM, may be associated with an increased risk of dementia.[24] Another meta-analysis concluded anti-HSV IgM was associated with an increased risk of developing AD.[25] Conflicting evidence is reported regarding the association of anti-HSV IgG antibodies and AD, demonstrating a lack of conclusive evidence of the effect of HSV antibodies on the risk of forms of dementia.[24,26-28]

Apolipoprotein E4 (APOE-ε4), a protein involved with fat metabolism, is widely recognized as the strongest genetic risk factor for developing AD.[29] Multiple studies have found that a history of both APOE-ε4 and HSV-1 infection is more prevalent in patients with AD and leads to a greater risk of developing AD compared with only one of these factors.[30-32] These results suggest APOE-ε4 and HSV-1 may interact synergistically in the brain and may lead to an increase in the pathognomonic amyloid plaque formation and deposition linked to acceleration of cognitive decline.[31]

Our findings suggest that daily antiviral treatment for OMC-HSV infections could serve as a preventive measure against AD and dementia. Given the overall safety profile and minimal side effects associated with long-term antiviral therapy, use in HSV-infected patients should be strongly considered to reduce the risk of AD and dementia.[33]

Definitive guidelines for OMC-HSV prophylaxis are lacking. Individuals with subclinical or asymptomatic OMC-HSV infections may benefit from daily viral suppression.[34] Our findings indicate that viral suppression significantly lowers the risk of AD and dementia, underscoring the need for updated, more inclusive prophylactic guidelines. Many HSV antiviral medications have been used for decades, and are well-tolerated, safe, and inexpensive, with few side-effects even up to 10 years of use.[33,35] Clinicians may consider obtaining genetic testing for APOE-ε4 in patients infected with oral or mucocutaneous HSV to further stratify risk and help guide the decision to treat patients with antivirals.

Our findings align with previous reports showing reduced AD and dementia incidence among herpes-infected patients treated with antivirals.[16,17,36] Strengths of this study include the large and diverse patient population from the TriNetX database, allowing robust subgroup analyses of OMC-HSV infections. However, establishing a direct causal link remains challenging due to potential confounding factors. Limitations include an inability to specify patients' antiviral regimens or treatment frequency, potential dementia subtype misclassification due to reliance on ICD-10 codes, and the use of certain ICD codes (ICD B-00.1, B-00.8, B-00.9) without precise anatomic localization, although predominantly oral and mucocutaneous. However, these codes were classified as OMC infections in our study based on their predominant occurrence at these sites.[19] Additionally, TriNetX does not specify if HSV infections are seropositive for HSV-1 or HSV-2. This may be important as it is unclear if a specific HSV serotype is associated with AD and dementia.

The findings of this study highlight the need for further research to stratify the risk of the development of AD and dementia based on dosage and length of antiviral treatment in OMC-HSV patients. Our findings did not suggest an increased risk of developing AD or other forms of dementia in anogenital HSV patients with or without antiviral medications. This discrepancy may be attributed to anogenital HSV infections residing within the coccygeal and sacral plexus of the dorsal root ganglia.[37] Given that these ganglia are more distal from the brain compared with the trigeminal ganglion, where oral HSV infections remain latent, the risk of AD and dementia may be influenced by the proximity of the HSV infection to the brain.[38] Consequently, both HSV-1 and HSV-2 may contribute to neurodegeneration when latent within the trigeminal ganglion, which is located near the brain. Future research should stratify HSV-1 and HSV-2 by infection site to validate this hypothesis.

CONCLUSION

The results of this cohort study demonstrate a significant association between antiviral treatment for OMC-HSV infections and a decreased incidence of AD and dementia compared with patients who did not receive antiviral treatment for OMC-HSV infections. Results did not indicate a significantly decreased risk of developing AD or other forms of dementia in anogenital HSV patients treated with antivirals compared with patients who were not treated with antivirals.

Dermatologists, often at the frontline of treating HSV infections, may find these results pivotal in shaping future clinical guidelines aimed at leveraging antiviral treatments as a preventative strategy against AD and dementia. These findings complement emerging evidence from herpes zoster vaccination studies and underscore the need for further investigation into antiviral prophylaxis as a feasible and scalable strategy to reduce the global burden of AD and related dementias.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.9616

March 2026 240 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Updates on Therapeutic Approaches for Management of Androgenetic Alopecia

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ABSTRACT

Androgenetic alopecia (AGA) is a common, progressive form of nonscarring hair loss, affecting both men and women. Its pathogenesis is largely driven by androgenic factors, including elevated dihydrotestosterone (DHT), leading to follicular miniaturization. While FDA-approved treatments like minoxidil and finasteride are standard, off-label therapies and emerging treatments continue to evolve. This systematic review examines the current and emerging treatment landscape for AGA, focusing on various topical, oral, injectable, and non-pharmacological interventions.

J Drugs Dermatol. 2026;25(3):240-245. doi:10.36849/JDD.9616

INTRODUCTION

Male androgenetic alopecia (AGA) and female pattern hair loss (FPHL) are common nonscarring hair loss disorders characterized by progressive scalp thinning, affecting up to 50% of men and women.[1] In men, it typically begins with bitemporal recession and crown thinning, while women often present with diffuse thinning and central part widening. Variability exists, with some women also exhibiting vertex or bitemporal involvement.

AGA is driven by dihydrotestosterone (DHT), which shortens the anagen phase and causes follicular miniaturization. Current FDA-approved treatments, topical minoxidil and oral finasteride require long-term use, have a delayed onset, and can trigger initial shedding, often limiting adherence. Notably, the role of androgens is not clear in female androgenetic alopecia. Female AGA may progress more slowly, often with preserved frontal hairlines and normal androgen levels, necessitating careful differential diagnosis and tailored management approaches.[2]

While these agents remain first-line, a range of off-label and emerging therapies are being investigated with promising results. This review summarizes established and investigational treatments for AGA and their clinical efficacy.

DISCUSSION

Topical Therapies

Topical Minoxidil

To date, topical minoxidil is one of the most commonly used medications to treat AGA. Its therapeutic effect is believed to involve several complementary mechanisms, including vasodilation, modulation of local inflammation, indirect antiandrogenic effects, and activation of the Wnt/β-catenin signaling pathway, which plays a key role in hair follicle regeneration. Minoxidil may also alter hair cycle dynamics by extending the anagen phase and shortening telogen.[3] Minoxidil 2–5% topical solution has been shown to increase hair count and density compared to placebo when applied twice daily.[4,5,6] In men with androgenetic alopecia, 5% topical minoxidil demonstrated greater efficacy over 48 weeks compared to 2% minoxidil and placebo, with earlier and more substantial improvements in non-vellus hair count, scalp coverage, and perceived treatment benefit.[4] Patients using the 5% formulation also reported enhanced quality of life and more favorable psychosocial perceptions of hair loss.[4] Increased rates of pruritus and local irritation were observed with the higher concentration in this study.4 Despite its widespread use, response rates to topical minoxidil remain variable. Approximately 60% of male AGA patients are classified as non-responders. This variability is thought to be linked to scalp sulfotransferase activity, which is essential for converting minoxidil into its active form. The follicular sulfotransferase assay (FSA) has emerged as a promising biomarker to predict treatment response prior to initiating therapy.[3]

Topical Anti-androgens

Topical antiandrogens aim to locally inhibit androgen activity while minimizing systemic side effects. Topical finasteride, a type II 5α-reductase inhibitor, reduces dihydrotestosterone (DHT) at the follicular level, mitigating the miniaturization process central to androgenetic alopecia (AGA).[7] Other agents, such as topical flutamide, have also shown efficacy. In a comparative study

of 40 patients, Faghihi et al found that 2% topical flutamide significantly improved hair density and thickness compared to minoxidil alone, with no reported systemic side effects and higher patient satisfaction scores.[8]

Combining topical antiandrogens with minoxidil represents a mechanistically complementary approach, targeting both androgen-mediated follicular regression and vascular insufficiency. In a randomized trial of 139 men with AGA, Asad et al (2024) found that topical finasteride plus minoxidil led to an 86.7% response rate compared to 69.1% with minoxidil monotherapy, with greater gains in hair count and density.[7] Similar results were reported by Rossi et al (2024), who observed significantly higher hair density in the combination group at both 3 and 6 months.[9] Importantly, neither study reported significant systemic side effects, supporting the safety of topical finasteride in combination regimens.[7,9] While promising, the small sample sizes and short trial durations limit conclusions about long-term outcomes. In April 2025, however, the US Food and Drug Administration (FDA) issued a statement emphasizing that no topical formulation of finasteride is currently approved and that the safety and efficacy of compounded products remain unproven.[10]

Topical Cetirizine

Cetirizine, a selective H_1-receptor antagonist traditionally used for allergic disorders, has emerged as a novel topical intervention for AGA. Its mechanism involves dual prostaglandin modulation, which downregulates hair growth-inhibiting prostaglandin D_2 (PGD_2) while simultaneously enhancing the production of hair growth-promoting prostaglandin E_2 (PGE_2).[11]

Two key studies provide clinical evidence for cetirizine's efficacy. Chen et al (2022) conducted a double-blind RCT (n = 85) demonstrating that 1% topical cetirizine significantly improved hair density compared to placebo, though its efficacy fell short of conventional minoxidil therapy.[11] Bassiouny et al (2023) found in their randomized, investigator-blinded trial (n = 64) that combining cetirizine with minoxidil produced significantly greater improvements in both terminal and vellus hair density compared to minoxidil monotherapy.[12] While cetirizine monotherapy demonstrates modest efficacy in AGA treatment, current evidence suggests its optimal clinical utility lies in combination therapy with established interventions such as minoxidil.

Oral Non-hormonal Therapies

Oral Minoxidil

The transition from topical to oral minoxidil offers an advanced therapeutic option for androgenic alopecia by providing systemic distribution that enhances blood flow to the scalp and prolongs the anagen phase.[13] Evidence suggests that oral minoxidil, especially at low doses (0.25–5 mg), may offer better follicular penetration than topical formulations. A systematic review by Rosenthal et al showed dose-dependent efficacy, with 0.25 mg being as effective as topical minoxidil.[13] Penha et al found that 5 mg oral minoxidil resulted in superior vertex hair density (+23.4 hairs/cm^2) compared to topical minoxidil (+5.5 hairs/cm^2).[14] In female pattern hair loss, Nascimento et al reported that 1 mg oral minoxidil outperformed 0.25 mg.[15] Oral therapy may benefit patients with poor adherence, scalp sensitivity, or limited response to topical treatments. However, it requires careful consideration due to potential cardiovascular adverse events and common side effects like hypertrichosis.[13-15]

Nutraceuticals

Nutraceutical strategies for AGA target inflammatory and androgenic pathways using bio-optimized botanicals like saw palmetto, curcumin, ashwagandha, and tocotrienols.[16] Clinical evidence for nutraceutical efficacy comes primarily from studies of standardized formulations. In a randomized, double-blind, placebo-controlled trial of a nutraceutical involving marine cartilage peptides, Bhatia et al demonstrated significantly higher rates of improved hair growth in the treatment group compared to placebo (79% vs 51%).[16] The study documented progressive improvements in hair quality parameters, including brittleness, dryness, and texture, at 180 days.[16] Patient-reported outcomes were similarly favorable, with 85% of users reporting a perceived reduction in hair loss compared to 55% in the placebo group.[16] Adverse effects were minimal, with only mild gastrointestinal symptoms reported in 3% of participants and no severe adverse events documented.[16] However, the absence of FDA regulation, inconsistent formulation standards, and limited head-to-head comparisons with pharmaceuticals limit broad clinical adoption. Additional research is needed to define dosing, assess long-term outcomes, and validate efficacy across diverse patient populations.[16]

Oral Hormonal Therapies

Finasteride

The therapeutic landscape of androgenic alopecia has been significantly shaped by selective 5α-reductase inhibition. Finasteride is a type II 5α-reductase used to inhibit the conversion of testosterone to dihydrotestosterone.[17] Finasteride demonstrates consistent efficacy at 1 mg daily, with randomized controlled trials supporting significant improvements in hair count and cosmetic outcomes.[17] The recent development of topical formulations offers comparable benefits with potentially reduced systemic exposure, though standardization of preparations remains an ongoing challenge. Recently, the FDA issued a safety alert highlighting potential risks linked to compounded topical finasteride products, including sexual dysfunction and inadvertent exposure risks for individuals of childbearing potential. The statement served as a reminder that no FDA-approved topical products currently contain finasteride, alone or in combination. These products have not been evaluated by the FDA for safety, efficacy, or quality, and adverse events.[10]

Dutasteride

Dutasteride, through dual inhibition of type I and II 5α-reductase isoenzymes, demonstrates enhanced efficacy compared to finasteride in controlled trials.[17] Meta-analytic evidence indicates superior improvements in both hair count and thickness with dutasteride 0.5 mg, particularly noteworthy in patients under 50 years of age.[17] Suppression of DHT with oral 5α-reductase inhibitors is associated with an approximately 1.57-fold increased risk of sexual adverse effects.[17] Common sexual side effects include decreased libido, erectile dysfunction, and ejaculatory dysfunction, while non-sexual adverse effects may include headache, upper respiratory tract infection, and abdominal discomfort.[17] Although most comparative studies report that both agents are generally well tolerated with similar safety profiles, one trial observed a higher incidence of sexual dysfunction with dutasteride, whereas others found no significant difference between the two.[17] Despite its clinical efficacy, the lack of FDA approval for the treatment of androgenetic alopecia limits dutasteride's broader clinical use.

Spironolactone

Spironolactone works by blocking androgen receptors, but it also has an additional mechanism: reducing androgen production by inhibiting 5α-reductase and adrenal androgen synthesis.[18,19] This dual action makes it particularly effective in female pattern hair loss (FPHL) by lowering circulating dihydrotestosterone (DHT) levels and preventing follicular miniaturization.[18,19] Spironolactone demonstrates significant efficacy across both oral and topical formulations, with systematic reviews supporting oral dosing between 80–200 mg daily.[18] Recent comparative trials indicate enhanced outcomes when combining spironolactone with topical minoxidil compared to finasteride-based combinations, particularly in female patients demonstrating suboptimal response to conventional therapy.[19] The safety profile for spironolactone remains favorable, though oral administration may be associated with dose-dependent effects, including menstrual irregularities and postural hypotension.[18]

Bicalutamide

Antiandrogen interventions offer important therapeutic alternatives, particularly in female pattern hair loss. Bicalutamide represents an emerging option in the antiandrogen arsenal, showing promise in treatment-resistant cases. Bicalutamide inhibits androgen receptor binding in hair follicles, blocking dihydrotestosterone (DHT)-induced miniaturization and prolonging the anagen phase in AGA.[20] Clinical evidence demonstrates meaningful improvements in hair density and standardized assessment scores, with potentially superior tolerability compared to traditional antiandrogens.[20] Current data primarily reflects outcomes in combination therapy settings, highlighting the need for further investigation of monotherapy applications.

Injectable Therapies

Platelet-Rich Plasma

Platelet-rich plasma (PRP) offers a regenerative approach to androgenetic alopecia, it delivers growth factors that stimulate dermal papilla cells, enhance angiogenesis, prolong the anagen phase, and activate follicular stem cells; all particularly effective when combined with topical minoxidil.[13,21-23] Meta-analyses by Yao and Xiao report significantly improved hair density, thickness, and patient satisfaction with combination therapy, with response rates exceeding 85% in some populations.[22,23] Studies by Wei et al and Janaani et al confirm superior outcomes in density and photographic scores, though effects on hair diameter are inconsistent.[24,25] Variability in PRP preparation and protocols limits standardization.[24,25] The safety profile is favorable, with mild, transient pain, edema, and bleeding being the most common side effects. However, nearly all patients report some post-procedural discomfort.[25] Further studies are needed to define optimal protocols and assess long-term efficacy.

Mesotherapy

Mesotherapy involves intradermal microinjections of pharmacological agents into the scalp, enhancing drug bioavailability at the follicular level while minimizing systemic side effects.[26,27] Common formulations include 5α-reductase inhibitors, vasodilators, vitamins, peptides, and growth factors to promote hair growth and counter DHT-mediated miniaturization.[26,27] In a review of 11 studies, over 95% of patients reported satisfactory outcomes, but comparisons with minoxidil showed mixed results, where some studies showed increased hair count, while others did not.[26] In one RCT, mesotherapy with vitamins was preferred over minoxidil.[26]

Dutasteride mesotherapy, with its longer half-life and greater potency compared to finasteride, inhibits DHT locally, reducing the risk of sexual side effects. Kumar et al (2024) found it significantly improved hair count and anagen-phase percentage compared to placebo, with 62.8% of patients showing improvement.[27] However, rare side effects, including skin infections, paradoxical nonscarring alopecia and localized inflammatory reactions, require further study. The lack of standardized protocols and variable efficacy limits its use, and more trials comparing mesotherapy to established treatments are needed.

Botox

Botulinum toxin type A (Botox®) is an emerging adjunct for AGA, proposed to enhance scalp blood flow, relax muscles, reduce TGF-β1 signaling, and decrease sebum production.[28] A meta-analysis by Cheng et al (2025) found significant hair count increases (SMD = 1.02, $P<.05$), with 76% dermatologist-reported efficacy and 71% patient satisfaction.[29]Yu et al (2024) showed that Botox combined with minoxidil improved photographic scores,

satisfaction, and quality of life versus minoxidil alone.[30] Li et al (2024) observed early follicular thickening on trichoscopy within 3 months (P<0.05).[31] Despite promising results, Botox protocols vary widely in dose (30–300 units), sites, and frequency, limiting standardization.[29] Safety is generally favorable, though rare reports suggest a possible link to frontal alopecia.[29] Further large-scale trials are needed to refine treatment regimens and confirm long-term safety.

Non-Surgical, Non-Drug Therapies

Low-level light therapy

Low-level light therapy (LLLT) treats androgenetic alopecia via photobiomodulation, enhancing mitochondrial activity, and ATP production, and reducing oxidative stress to promote anagen initiation and prolong hair growth.[13,32] LLLT improves follicular blood flow and nutrient delivery, with the most benefit seen in early to moderate AGA. Meta-analyses of RCTs show laser combs (635–655 nm) and helmet devices increase terminal hair density by 10–30 hairs/cm^2 and hair shaft diameter by 10–20 µm after 16–24 weeks.[32] While effective alone, LLLT is often used in combination protocols, offering a non-pharmacologic option for patients unable to tolerate standard therapies.

Microneedle-Based Technologies

Microneedling (MN) enhances AGA treatment by increasing topical drug absorption and stimulating follicular regeneration through controlled microtrauma and neovascularization.[33-35] The stratum corneum limits the absorption of agents like minoxidil (0.3%–4.5%), but MN creates transient microchannels to improve delivery and promote hair growth.[33-35]

While effective alone, MN is often combined with topicals to boost efficacy. Recent innovations include light-guiding microneedle patches (LMNP), which pair mechanical stimulation with photobiomodulation. In a 24-week study, LMNP with red and green LED increased hair density by 21.93/cm^2 and 29.23/cm^2, respectively (P<0.001).[36] These findings highlight MN's potential as a minimally invasive adjunct in AGA therapy.

Energy-Based Interventions

Fractional laser therapy promotes follicular regeneration through controlled thermal injury, enhancing transdermal drug delivery and activating wound healing pathways.[37] Fractional CO_2 lasers combined with topical dutasteride have shown efficacy in moderate-to-advanced AGA, with 40% of patients showing good and 6.7% excellent improvement.[37] Although this study focused only on male androgenic alopecia, the statistically significant improvement in hair growth found in the fractional CO_2 laser combination group compared to the laser-only group, could be beneficial to female patients with AGA.[37]

Non-ablative fractional laser (NAFL) using a 1565 nm wavelength has also demonstrated clinical benefits. Hair counts increased from 164.93 to 196.27 hairs/cm^2 with NAFL versus 161.07 to 177.20 hairs/cm^2 with minoxidil (P=0.001), with greater gains in terminal hair density.[38] These findings support fractional laser therapy as a promising standalone or adjunctive option in AGA management. However, it is important to note that this study did not include skin of color patients.

Combination Strategies with Non-surgical Non-Drug Therapies

Non-pharmacologic modalities such as low-level light therapy (LLLT), microneedling (MN), and energy-based interventions have been increasingly studied in combination with conventional therapies for androgenetic alopecia. LLLT enhances mitochondrial function, increases ATP production, and modulates oxidative stress, promoting anagen initiation and prolonged follicular activity.[33] When used alongside agents like minoxidil or finasteride, it has been shown to improve treatment outcomes.[33] Microneedling improves transdermal drug delivery by creating transient microchannels in the skin and stimulates endogenous growth factors and neovascularization.[33-36] Studies have shown that combining MN with topical therapies can significantly enhance hair density and thickness.[36] Energy-based therapies such as fractional CO_2 and non-ablative fractional lasers operate through enhancement of transdermal delivery systems and activation of wound healing cascades.[37,38] Clinical trials have demonstrated that combining these interventions with topical treatments, including dutasteride, may lead to greater improvements in terminal hair parameters than monotherapy alone.[37,38] These approaches represent promising adjuncts to medical therapy, particularly for patients with early-to-moderate AGA or incomplete response to standard treatments.

Emerging Therapies

Stem Cell-Derived Exosomes and Growth Factor Formulations

Stem cell-derived therapies, especially exosomes, show promise for AGA by supporting dermal papilla cell activity and activating Wnt/β-catenin signaling. In a 24-week study, Lee et al reported a density increase of 8.10 hairs/cm^2 with exosome treatment.[39,40] These products are not FDA-approved, largely due to concerns over manufacturing consistency, donor variability, and long-term safety. Other stem cell-based options include ADSC-CM and hUC-MSC-CM, both of which improved hair density and thickness over 16 weeks without adverse effects.[41] ADSC-CE also showed benefit, with a 28.1% increase in hair count and a 14.2% increase in thickness in 8 weeks (P<0.05).[41] Delivery methods like microneedling or fractional lasers may enhance efficacy.[39] Standardization and further safety data are needed before widespread use.

Antibody-Based Therapies and Long-Acting Agents

The prolactin receptor antibody HMI-115 has shown increased hair density without major side effects in a phase 1b trial.[42] Other investigational targets include IL-6, CXCL12, and DKK1, all involved in follicular signaling pathways.[19] Long-acting injectable

finasteride is also in development to improve adherence and minimize systemic exposure.[19] While biologics may reduce dosing frequency and GI side effects, barriers include cost, access, and limited long-term data.[19] Ongoing trials will clarify their clinical utility.[19,42]

Combining Emerging and Established Therapies

Combining emerging therapies with standard treatments may enhance results. Exosome formulations paired with microneedling or minoxidil have shown improved outcomes.[39] Long-acting finasteride could be used with LLLT or topical agents to improve efficacy and convenience.[19,42] These strategies may benefit patients with suboptimal responses to monotherapy and support more personalized AGA management.

CONCLUSION

Androgenetic alopecia remains a complex condition with a growing array of therapeutic options that extend beyond traditional FDA-approved agents. While topical and oral minoxidil, along with finasteride, remain foundational, recent advances highlight the potential of oral non-hormonal therapies, antiandrogens, injectables like PRP and mesotherapy, and novel modalities such as low-level light therapy and microneedling. Emerging evidence supports the use of combination regimens to improve efficacy and patient satisfaction. However, variability in study design, treatment protocols, and outcome measures across trials limits direct comparisons. Continued research is needed to optimize therapeutic algorithms, establish standardized protocols, and identify predictors of response to guide individualized treatment strategies.

DISCLOSURES

Dr Tiffany Mayo has served as an investigator for Acelyrin, Bristol Myers Squibb (BMS), Galderma, Janssen, Eli Lilly, and Pfizer. She has also served as a consultant for AbbVie, Arcutis, BMS, Bodewell, Janssen, Lilly, LEO Pharma, Merck, Novartis, Pfizer, Takeda, and UCB. Aaliyah Bourne and DanTasia Welch have no disclosures.

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doi:10.36849/JDD.9664

March 2026 246 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Eyebrow Madarosis: An Updated Review of the Etiology and Management, Part I – Nonscarring Disorders

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ABSTRACT

Background: Eyebrow madarosis, or eyebrow alopecia, has significant cosmetic and psychosocial implications. Nonscarring causes are diverse, including autoimmune, infectious, endocrine, genetic, nutritional, traumatic, and iatrogenic etiologies. Despite its frequency in dermatologic practice, guidance for evaluation and management remains limited.

Methods: A comprehensive PubMed search (1960–2025) was performed using terms related to "eyebrow alopecia," "eyebrow madarosis," and specific disease processes. English-language studies were included if they evaluated eyebrow involvement and provided data on etiology, diagnosis, or treatment. Review articles without new patient data and studies limited to scalp alopecia were excluded.

Results: Nonscarring eyebrow alopecia can be caused by autoimmune disorders such as alopecia areata, infections including syphilis and tinea faciei, endocrinologic conditions like hypothyroidism, and inflammatory dermatoses such as atopic or seborrheic dermatitis. Additional causes include nutritional deficiencies, trauma, and drug-induced alopecia. Reported treatments include corticosteroids, calcineurin inhibitors, JAK inhibitors, immunomodulators, antifungals, zinc supplementation, and behavioral therapy. Novel agents such as dupilumab and roflumilast have shown promise for inflammatory-related eyebrow loss.

Conclusion: Nonscarring eyebrow madarosis encompasses a wide range of reversible causes. Early recognition and targeted therapy can lead to eyebrow regrowth and improve psychosocial outcomes. Further studies are needed to establish evidence-based treatment algorithms and validated tools to assess eyebrow regrowth.

J Drugs Dermatol. 2026;25(3):246-250. doi:10.36849/JDD.9664

INTRODUCTION

The eyebrows are central to facial expression and identity, serving both cosmetic and functional purposes.[1,2] Their short anagen phase of approximately two to three months and slow growth rate of 0.12–0.15 mm per day distinguish them from scalp hair.[3,4] While eyebrow density is typically stable, aging contributes to thinning and whitening, though some men may develop increased fullness.[5] Beyond age-related changes, a variety of underlying conditions can contribute to eyebrow loss. Eyebrow loss, or madarosis, may be complete or partial and is classified as scarring or nonscarring.[6] Because eyebrows are so closely tied to appearance and self-identity, eyebrow loss often results in disproportionate psychosocial distress.[7] This review summarizes nonscarring causes of eyebrow alopecia and current treatment approaches.

MATERIALS AND METHODS

A comprehensive literature review was conducted to evaluate the clinical evidence related to the causes, diagnostic features, and management of eyebrow madarosis. Studies were identified using PubMed searches performed in August 2025 (1960–2025) with keywords including "eyebrow alopecia," "eyebrow madarosis," "eyebrow loss," "alopecia areata eyebrow," "frontal fibrosing alopecia eyebrow," "eyebrow hypothyroidism," "eyebrow chemotherapy alopecia," and other etiology-specific terms. Articles were included if they met the following criteria: English-language or English translation available; original studies (including case reports, case series, retrospective or prospective reviews, or clinical trials); and explicit evaluation of eyebrow involvement in alopecia or systemic disease. Studies were excluded if they were review articles without new patient data, expert opinions or commentaries, non-English without translation, or focused exclusively on scalp alopecia without eyebrow-specific outcomes. Each study was assessed for details regarding etiology of eyebrow alopecia, diagnostic methods, interventions, and treatment outcomes. For Part I, analysis was limited to nonscarring causes of eyebrow alopecia, and etiologies were further subcategorized by underlying disease process.

RESULTS ANDF DISCUSSION

Autoimmune

Alopecia Areata

Alopecia areata (AA) is a frequent cause of nonscarring eyebrow loss, typically presenting with bilateral patchy alopecia (Figure 1).[8] Trichoscopy can be a useful tool when the etiology is unclear, demonstrating exclamation point hairs, cadaverized hairs, and yellow dots.[8,9] Several assessment tools have been developed, including clinician-reported outcomes (ClinRO), patient-reported outcomes (PRO), and the Brigham Eyebrow Tool for Alopecia Areata (BETA) to assign severity.[10] Although no standard treatment has been established, multiple therapeutic approaches aimed at reducing inflammation have been reported. Intralesional triamcinolone acetonide (ILTAC) at a concentration of 2.5 mg/mL, with 0.5 mg injected into each eyebrow every four to six weeks, has shown regrowth.[11] Although not specifically approved for eyebrow alopecia areata, oral JAK inhibitors have demonstrated efficacy, with baricitinib 4 mg producing at least a two-point improvement in ClinRO eyebrow scores in two phase 3 randomized controlled trials,[12] and tofacitinib 15 mg leading to complete eyebrow regrowth in 34.5% of patients.[13,14] Topical JAK inhibitors are also effective; in one study, 2% tofacitinib gel applied twice daily resulted in partial or complete regrowth in 66.7% (12/18) of patients, while ruxolitinib 0.6% cream led to complete eyebrow regrowth after 12 weeks in a case report.[15] Non-pharmacologic approaches include pulsed diode laser therapy at 904 nm, which achieved complete eyebrow regrowth in five out of six patients with recalcitrant AA after four treatment sessions.[16] Additionally, topical immunotherapy with diphenylcyclopropenone (DPCP) has shown promise, particularly when combined with prior anthralin application, resulting in complete regrowth of eyebrows and eyelashes in 16.7% of patients treated with DPCP alone and in 66.7% of those receiving combination therapy.[17]

FIGURE 1. Alopecia Areata presenting with patchy eyebrow loss. Partial eyebrow alopecia displaying bilateral patchy thinning of the eyebrows.



Infectious

Bacterial

Infectious etiologies are an important consideration in eyebrow madarosis. Syphilis, for example, can present with patchy lateral eyebrow loss during the secondary stage, a feature often referred to as the "omnibus sign."[18,19] In two case reports, treatment with benzathine penicillin G resulted in complete eyebrow regrowth.[20]

Fungal

Dermatophyte infections, such as tinea faciei, may also involve the eyebrows, producing partial alopecia accompanied by pink-to-red scaly patches and plaques. In these cases, eyebrow loss has been shown to be reversible following treatment with topical or oral antifungal agents.[21] One report described resolution after two weeks of systemic terbinafine combined with topical application of 1% naftifine-0.25% ketoconazole[22]; while a case series reported successful outcomes with griseofulvin 1000 mg/day in two patients and terbinafine 250 mg/day in four patients each paired with topical antimycotics for 8 weeks, resulting in resolution and mycological cure.[23]

Viral

Another infectious cause is trichodysplasia spinulosa, a rare disorder linked to polyomavirus infection in immunocompromised individuals, which is characterized by spiny follicular papules and may cause profound nonscarring eyebrow loss.[24] Reported management strategies include topical cidofovir, oral valganciclovir, and reduction of immunosuppression, though their effect on eyebrow regrowth has not been clearly documented. Finally, varicella zoster virus more commonly results in eyelash loss, although eyebrow involvement is rare (Figure 2).[25]

FIGURE 2. Herpes zoster ophthalmicus with eyebrow involvement. Partial eyebrow alopecia with overlying yellow scale and erosions in the V1 dermatome.



Endocrinologic

Hypothyroidism is a well-recognized endocrinologic cause of eyebrow madarosis, classically presenting with loss of the lateral third of the eyebrows, known as Hertoghe's sign or the Queen Anne sign.[26,27] While adequate thyroid hormone replacement is thought to restore normal telogen–anagen hair cycling, the specific response of eyebrow alopecia to thyroxine therapy has not been well documented in the literature.

Genetic

Several genetic disorders are associated with eyebrow madarosis. Ectodermal dysplasia, a heterogeneous group of inherited conditions affecting hair, teeth, nails, and sweat glands, frequently present with sparse or absent eyebrows, sometimes in

association with eyelash loss, hypodontia, and hypohidrosis.[28,29] Hereditary hypotrichosis, a rare congenital disorder of hair development, may manifest as diffuse thinning of the eyebrows in childhood, often accompanied by reduced scalp and body hair.[30] In addition, certain syndromic immunodeficiencies, such as T-cell immunodeficiency with congenital alopecia and nail dystrophy, have been reported to include eyebrow loss as part of their phenotype. In these conditions, treatment options remain limited, with management focused primarily on supportive cosmetic measures rather than restoration of hair growth. Lamellar ichthyosis, a rare disorder of keratinization, has also been associated with eyebrow loss. In this condition, treatment with Dr Michaels® product family, which combines topical and oral herbal therapies, was associated with eyebrow regrowth in reported cases.[31] Ultimately, management is largely supportive, focusing on emollients and keratolytic agents, although eyebrow regrowth is not commonly documented.

Chronic Inflammatory Skin Diseases

Atopic Dermatitis

Atopic dermatitis (AD) is frequently associated with eyebrow involvement, most notably Hertoghe's sign, or thinning of the lateral third of the eyebrows (Figure 3). This finding has been reported in up to 39% of patients with AD.[32] An unusual presentation of unilateral thinning of the entire eyebrow has also been described in a 21-year-old male with late-onset AD.[33] In another case, a 15-year-old male experienced partial eyebrow regrowth after two months of treatment with emollients and topical corticosteroids, with improvement in facial eczema.[34] More recently, a 49-year-old woman with severe AD and alopecia universalis received dupilumab, and after eight months she experienced full scalp hair regrowth and some eyebrow hair regrowth, suggesting that systemic IL-4/IL-13 blockade may promote eyebrow regrowth when AD coexists with alopecia universalis.[35]

FIGURE 3. Atopic dermatitis with Hertoghe's Sign. Thinning of the lateral third of the eyebrows in a patient with active atopic dermatitis.



Seborrheic Dermatitis

Seborrheic dermatitis (SD), a chronic inflammatory skin disorder, can present with erythema and scaling of the eyebrows, sometimes leading to eyebrow loss secondary to persistent pruritus.[36] Although not specific to eyebrows, treatment of facial SD focuses on reducing Malassezia colonization with topical antifungals (ketoconazole, ciclopirox, clotrimazole) and controlling inflammation with topical corticosteroids or topical calcineurin inhibitors (desonide, hydrocortisone, lithium succinate/gluconate, topical pimecrolimus/tacrolimus) and more recently FDA-approved roflumilast 0.3% foam, which reduces scaling and allows partial regrowth of eyebrow hairs.[36,37] In severe or treatment-resistant cases, the use of systemic antifungal drugs (terbinafine, itraconazole), as well as UVB phototherapy, may also be considered.[37] Roflumilast, a phosphodiesterase-4 inhibitor, has demonstrated significant efficacy in treating seborrheic dermatitis of the scalp, face, and trunk with 79.5 % of roflumilast treated patients achieving clear or almost clear skin within eight weeks of daily use in a randomized phase 3 trial.[38] Although these studies did not specifically evaluate eyebrow involvement, the reduction of inflammation is likely to support regrowth.

Follicular Mucinosis

Follicular mucinosis (FM) is a rare condition characterized by follicular papules and indurated plaques leading to nonscarring alopecia, with eyebrow loss sometimes appearing as an early clinical sign. FM can occur as a primary benign idiopathic condition, with either an acute or chronic course, or as a secondary disorder associated with various benign and malignant conditions, including cutaneous lymphomas.[40] The pathogenesis is not completely understood, and no single treatment option has proven consistently effective. In one report, a 10-year-old developed lateral eyebrow alopecia as the first manifestation of FM.[39] Another case described a 51-year-old man with idiopathic FM who had indurated facial papules and loss of the outer one-third of both eyebrows. After failing multiple therapies (topical and systemic corticosteroids, hydroxychloroquine, mycophenolate mofetil), he achieved complete clearance of lesions and eyebrow regrowth within one month of starting dupilumab.[41] These findings suggest that IL-4/IL-13 blockade may be effective for FM-associated brow loss.

Nutritional

Zinc deficiency is a recognized nutritional cause of eyebrow madarosis and may present in the setting of acrodermatitis enteropathica.[42] Oral zinc supplementation typically results in improvement of hair growth, including the eyebrows. One report described a patient with chronic diarrhea due to sucrase deficiency who developed thicker and more pigmented eyebrows after zinc 40 mg daily repletion.[43] Zinc repletion is typically combined with copper supplementation, 8–15 mg of zinc for every 1 mg of copper, to prevent copper deficiency.

Traumatic

Trichotillomania is a traumatic cause of nonscarring eyebrow alopecia, typically presenting as isolated eyebrow loss with

broken hairs visible on dermoscopy.[44] Management primarily involves behavioral and psychiatric interventions such as psychotherapy, though pharmacologic approaches have also been explored. N-acetylcysteine (NAC), administered at doses of 1200 to 1800 mg per day,[45] has shown benefit for scalp hair regrowth in case reports; however, eyebrow regrowth appears limited. In a case study, six months of treatment with NAC 1,200 mg/day improved scalp but did not result in eyelash or eyebrow regrowth.[46]

Iatrogenic

Chemotherapy

Chemotherapy is a well-recognized cause of eyebrow madarosis. In a prospective observational study, 82.4% of patients treated with fluorouracil, epirubicin, cyclophosphamide (FEC), and taxane-based regimens developed eyebrow loss.[47] The agents most implicated include taxanes, doxorubicin, and cyclophosphamide. Eyebrow regrowth may occur more rapidly in younger patients; however, loss can persist and, in some cases, become permanent. In a longitudinal cohort of breast cancer survivors, 89% of chemotherapy recipients reported eyebrow loss, with 32% describing complete loss.[48] Currently, no standardized management or preventive strategy exists for chemotherapy-induced eyebrow loss, though approaches such as scalp cooling, cryotherapy, and topical vasoconstrictors could be promising preventative options.[49,50]

Endocrine Therapy

Endocrine therapy, particularly with selective estrogen receptor modulators (SERMs) and aromatase inhibitors, has also been associated with eyebrow and eyelash alopecia. In a retrospective cohort study, 28.3% of patients receiving endocrine therapy developed eyebrow or eyelash involvement.[51] Management options remain limited, and regrowth is often incomplete.

Atomoxetine

Drug-induced eyebrow loss has also been reported with atomoxetine, a selective norepinephrine reuptake inhibitor (NRI). In a case report, an eight-year-old girl developed increasingly sparse eyebrows after starting atomoxetine for attention-deficit/hyperactivity disorder.[52] Discontinuation of the medication resulted in regrowth, emphasizing the importance of considering iatrogenic causes in the differential diagnosis of eyebrow alopecia.

Toxicity

Chronic hypervitaminosis A has been implicated in eyebrow madarosis, with loss typically reversible upon reduction or cessation of vitamin A intake. Systemic mastocytosis has also been associated with eyebrow alopecia, sometimes accompanied by leonine facies, although treatment effects on eyebrow regrowth have not been described.[53] Substance abuse can also contribute to eyebrow loss; in one case, bilateral eyebrow alopecia developed in the context of chronic cocaine use, with complete reversal following abstinence.[54]

CONCLUSION

Eyebrow madarosis can be due to various nonscarring conditions, with management strategies tailored to the underlying etiology. Treatment focuses on identifying and addressing reversible causes to restore follicular function and promote regrowth. Therapeutic options include corticosteroids, immunomodulators, JAK inhibitors, oral minoxidil, prostaglandin analogs, and laser or light-based therapies. Most evidence derives from case reports and small series, with few randomized trials, underscoring the need for controlled studies and validated eyebrow-specific assessment tools.

DISCLOSURES

JN is supported by an AbbVie Medical Student Fellowship Grant. AF has no conflicts of interest to disclose.

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doi:10.36849/JDD.9712

March 2026 251 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Persistent Alopecic Patches Following Dutasteride Mesotherapy for Female Androgenetic Alopecia: A Case Series

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ABSTRACT

Background: Androgenetic alopecia (AGA) is the most common cause of hair loss. To minimize systemic adverse effects of 5-alpha-reductase inhibitors, dutasteride mesotherapy has gained popularity. Although generally considered safe, alopecia at injection sites has been increasingly reported. We describe three cases of persistent alopecia following dutasteride mesotherapy in women with AGA.

Case Reports: Three female patients with AGA underwent mesotherapy with dutasteride (0.025–0.05%). Case 1: A 44-year-old woman developed multiple alopecic patches 1 month after a single session, with trichoscopic and histologic features of scarring alopecia. Only partial improvement occurred, and surgical correction was later required. Case 2: A 30-year-old woman developed 4 alopecic patches after 2 sessions. Trichoscopy revealed mixed features of cicatricial alopecia and follicular miniaturization, with limited regrowth despite optimized medical therapy. Case 3: A 48-year-old woman developed numerous alopecic patches 3 months after a single session. Follicular openings were preserved, and miniaturized hairs predominated. Alopecia persisted long-term despite corticosteroids and adjunctive treatments.

Discussion: Reported cases of alopecia after mesotherapy include both scarring and non-scarring patterns, suggesting diverse mechanisms, such as mechanical injury, cytotoxicity from solvents, inflammation, or infection. In this series, none of the patients experienced full regrowth, highlighting the potential for lasting aesthetic sequelae. Published cases show similar variability but often lack detailed trichoscopic or procedural information, limiting interpretation. These findings underscore the importance of proper counseling, careful technique, and close follow-up when using dutasteride mesotherapy. This complication may be underrecognized, and clinicians should maintain vigilance for early detection and management.

J Drugs Dermatol. 2026;25(3):251-255. doi:10.36849/JDD.9712

INTRODUCTION

Androgenetic alopecia (AGA) is the most prevalent form of hair loss worldwide, affecting both men and women, with an estimated prevalence of up to 80% in males and approximately 40% in females, at some point of their lives.[1] Its multifactorial etiology involves genetic predisposition and androgenic hormonal influences, primarily dihydrotestosterone (DHT), which acts on susceptible hair follicles. The central pathological mechanism is follicular miniaturization, with progressive hair shaft thinning and eventual hair loss.[2]

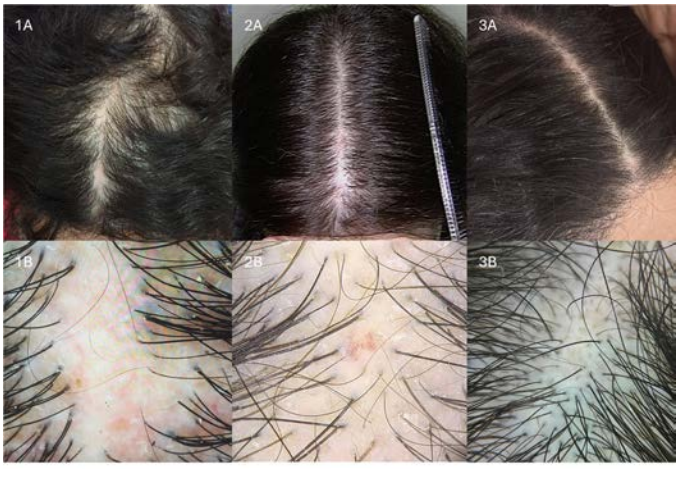
Recently, an expanding armamentarium of therapeutic options has become available, including systemic and topical pharmacological agents as well as procedural interventions such as mesotherapy, platelet-rich plasma (PRP), and hair transplantation. Among pharmacological treatments, 5-alpha-reductase inhibitors, such as finasteride/dutasteride, have demonstrated efficacy by reducing DHT levels. However, systemic administration is often limited by potential adverse effects, including decreased libido and gynecomastia, and contraindications, such as pregnancy/lactation.[3] To mitigate these effects, alternative administration routes, such as localized scalp injections (mesotherapy), have gained popularity. Mesotherapy with dutasteride is increasingly performed, with treatment frequency ranging from once per week to once every 3 months, typically using concentrations from 0.005% to 0.05%.[4] However, this technique is not devoid of complications. We report 3 cases of female patients with AGA who developed persistent alopecia following mesotherapy with dutasteride.

Clinical Cases

Case 1

The first case is a 44-year-old female with AGA and no relevant medical history, under oral finasteride 5 mg/day plus topical minoxidil 5%, and with a history of previous hair transplantation. The patient received a single session of mesotherapy with dutasteride (final concentration of 0.025%), mixed with an anesthetic solution (lidocaine, bupivacaine, adrenaline, and sodium bicarbonate). Treatment was administered using 4 mm, 30G needles, with 0.05–0.1 mL per site of injection and 1 cm spacing between injection sites, for a maximum total of 2 mL. The administration technique was similar in the cases described below.

FIGURE 1. Clinical (A, upper panels) and trichoscopic (B, lower panels) findings of cases 1, 2, and 3. Clinically, all patients showcased small patches of alopecia at some of the injection sites. Note the cicatricial nature of lesions on case 1 (1A). On trichoscopy, the lack of follicular openings and skin atrophy is prominent on the 1B, while on 3B, the follicular ostia are preserved, and follicular miniaturization is the predominant feature. The second case (2B) displays mixed findings, with central areas without follicular openings and also evident miniaturization.



One month after the procedure, the patient developed 8 small alopecic patches (0.3–0.5 cm in diameter) at injection sites (Figure 1, 1A). Clinical examination revealed areas of cicatricial alopecia, without erythema or scaling. Trichoscopy confirmed these findings, showcasing areas with smooth, porcelain-white skin and complete loss of follicular ostia; sparse telangiectasias were observed, and no signs of active inflammation were present, with absence of erythema or pustules, and only minimal perifollicular hyperkeratosis (Figure1, 1B). Treatment with clobetasol solution resulted in partial improvement, yet 4 alopecic patches persisted after 5 months. A skin punch biopsy showed mild epidermal acanthosis, reduction of adnexal structures in the dermis, and vertical fibrosis involving the previous pilosebaceous units, with a lymphocytic infiltrate around the isthmic region. A second hair transplantation was performed 1 year later to address these areas.

Case 2

A 30-year-old healthy female with AGA, under oral minoxidil 0.5 mg/day, spironolactone 100 mg/day, and topical minoxidil 5%, underwent 2 sessions of mesotherapy with 0.05% dutasteride (without anesthetic admixture), 8 weeks apart. One month after the second session, 4 alopecic patches appeared at injection sites (Figure 1, 2A). Trichoscopy showed both areas of cicatricial alopecia and follicular miniaturization (Figure 1, 2B). Treatment included clobetasol solution and optimization of systemic therapy, later adding finasteride 5 mg/day. Only partial regrowth was achieved. Two years later, the patient underwent hair transplantation for correction.

Case 3

Our last case is a 48-year-old female with AGA and seborrheic dermatitis, under topical minoxidil 0.5%. The patient preferred to avoid systemic therapies, and mesotherapy with dutasteride was proposed. She underwent a single session, with a final dutasteride concentration of 0.025% (mixed with an anesthetic solution, as described in case 1). Three months post-procedure, 18 alopecic patches were identified by the medical team in the treated areas. The patient was unaware of the lesions. Trichoscopy revealed preserved follicular openings, but with miniaturized or absent hairs. She received 2 sessions of intralesional corticosteroid injections, with limited improvement. Despite adjunctive therapies, including oral/topical minoxidil and PRP, the alopecic patches persisted after 4 years of follow-up (Figure 1, 3A), with no evidence of regrowth and with overlapping trichoscopic findings (Figure 1, 3B).

DISCUSSION

Previous descriptions of alopecia induced by cosmetic injectable procedures encompass both non-scarring and scarring alopecia. While mesotherapy is generally considered safe, at least 9 other cases of alopecia following this procedure have been reported, as summarized in Table 1.[5-9] Only 4 of these refer to solutions including dutasteride, as in our series. The interval between the last mesotherapy session and symptom onset varied, from a few days to several weeks, as did the clinical/trichoscopic findings, suggesting multiple possible pathogenic mechanisms.

Duque-Estrada et al (2009) documented 2 cases of paradoxical alopecia after mesotherapy with non-dutasteride agents, including one case with permanent cicatricial alopecia and the other with non-scarring alopecia and complete hair-regrowth during follow-up.[5] El-Komy et al (2017) described 3 patients who also developed alopecia at mesotherapy injection sites, each of whom displayed areas with absence of follicular ostia on trichoscopy, and only 2 of whom experienced partial hair regrowth over time.[6] Cura et al (2022) reported 2 additional cases of alopecia following mesotherapy with dutasteride.[7] One patient presented with cutaneous atrophy at injection sites and showed no short-term improvement, while the other patient was lost to follow-up. Even though the authors categorized their findings as non-scarring, trichoscopic findings at presentation of the second case included white dots and a reduced number of follicular openings, suggesting at least partial evidence of fibrosis and possible scarring disease.

In our series, the first case developed cicatricial alopecia at sites of injection, while our third case displayed preserved follicular ostia and follicular miniaturization. The second patient presented with mixed clinical/trichoscopic findings of cicatricial alopecia and follicular miniaturization; Interestingly, none of the 3 cases experienced complete regrowth over time, even with optimized medical therapy and when there were preserved follicular ostia.

TABLE 1.

Post-Mesotherapy Alopecia Reported Cases (Literature Review)

Authors	Sex	Age (years)	Procedure	Scalp Topography	Hair Loss Onset	Clinical Features at Diagnosis	Treatment	Outcome
Duque-Estrada et al	Female	32	Mesotherapy with mesoglycan	Right parietal	Few days	Single alopetic patch with edema and erythema, associated with trichodynia and paresthesias. Trichoscopy showed loss of follicular ostia.	Not specified	Permanent cicatricial alopecia
Duque-Estrada et al	Female	22	Mesotherapy with lilium compositum, solanum compositum, *Thuja* and *Tanacetum*	Parietal and vertex	Not specified	Three patches of alopecia with mild erythema. Trichoscopy showed preserved follicular ostia.	Not specified	Complete hair regrowth at 7 months of follow-up
El-Komy et al	Female	30	Mesotherapy with dutasteride and Insulin-like Growth Factor-1 (IGF-1), basic Fibroblast Growth Factor (bfGf), Vascular Endothelial Growth Factor (VEGF), Copper Tripeptide-1, Multi-vitamins, Amino acids and Minerals (Mesologica MRS Hair)	Frontal	1 week	Multiple slightly erythematous alopetic patches. Trichoscopy showed loss of follicular ostia and peri/interfollicular mild scaling.	Topical minoxidil (5%)	Partial hair regrowth at 5 months of follow-up; Areas of permanent cicatricial alopecia
El-Komy et al	Female	29	Mesotherapy with dutasteride and Insulin-like Growth Factor-1 (IGF-1), basic Fibroblast Growth Factor (bfGf), Vascular Endothelial Growth Factor (VEGF), Copper Tripeptide-1, Multi-vitamins, Amino acids and Minerals (Mesologica MRS Hair)	Frontal	Not specified	Single tender, erythematous and crusted alopetic plaque. Trichoscopy showed loss of follicular ostia and peri/interfollicular mild scaling, as well as several vellus hairs.	None	Permanent cicatricial alopecia at 8 months of follow-up
El-Komy et al	Female	34	Unspecified mesotherapy	Frontal midscalp	Not specified	Two linear erythematous depressed atrophic scars. Trichoscopy showed loss of follicular ostia, peri/interfollicular mild scaling and several vellus hairs.	Intralesional saline injection and topical melatonin	Partial hair regrowth at 3 months of follow up. Areas of permanent cicatricial alopecia
Cura et al	Female	42	Mesotherapy with dutasteride	Parietal and vertex	1 month	Focal patchy alopecia at mesotherapy injection site without atrophy, erythema, scaling, or local discomfort. Trichoscopy showed multiple white dots, decreased follicular openings and vellus hairs.	None	Loss of follow-up
Cura et al	Male	58	Mesotherapy with dutasteride	Frontal and parietal	Not specified	Bald atrophic patches at mesotherapy injection sites. Trichoscopy findings not described.	Topical minoxidil (5%)	Permanent alopecia at 3 months follow-up (likely cicatricial alopecia)
Al-Khalaf et al	Female	25	Mesotherapy with buflomedil, hydrochloride, pyridoxine hydrochloride, pantothenic acid, niacinamide, thiamine hydrochloride and acetylcysteine	Frontal and parietal	2.5 weeks	Scalp pain and diffuse hair loss. Trichoscopy showed findings of alopecia areata (Yellow dots, thinning of hair, coudability hairs, irregular diameters and exclamations mark hairs).	Oral, intralesional, and topical corticosteroids	Partial hair regrowth at 6 months follow-up
Kadry et al	Female	26	Mesotherapy with flavonoids, vitamins (B1, B3, B5, B6, B8 and C), procaine and saline	Right and left parietal	2 weeks	Scalp pain erythema and diffuse draining abscesses with overlying alopecia. Isolation of *Pseudomonas aeruginosa and Acinobacter*. No trichoscopy description.	Piperacillin/tazobactam + ciprofloxacin and surgical drainage	Permanent cicatricial alopecia
Case n°1	Female	44	Mesotherapy with dutasteride	Frontal and parietal	1 month	Multiple small cicatricial alopecic patches at injection sites without inflammatory signs Trichoscopy showed loss of follicular openings.	Topical corticosteroids; hair transplantation	Partial hair regrowth; areas of permanent cicatricial alopecia (before hair transplantation)

TABLE 1. (CONTINUED)

Post-Mesotherapy Alopecia Reported Cases (Literature Review)								
Authors	Sex	Age (years)	Procedure	Scalp Topography	Hair Loss Onset	Clinical Features at Diagnosis	Treatment	Outcome
Case n°2	Female	30	Mesotherapy with dutasteride	Frontal and parietal	1 month	Multiple small cicatricial alopecic patches at injection sites without inflammatory signs. Trichoscopy showed loss of follicular ostia and also follicular miniaturization.	Topical corticosteroids; oral finasteride; hair transplantation	Partial hair regrowth; areas of permanent cicatricial alopecia (before hair transplantation)
Case n°3	Female	48	Mesotherapy with dutasteride	Frontal and parietal	3 months	Multiple small alopecic patches at injection sites without inflammatory signs. Trichoscopy showed preserved follicular ostia and follicular miniaturization.	Intralesional corticosteroids, oral and topical minoxidil, platelet-rich plasma injections	Partial hair regrowth, with areas of permanent non-cicatricial alopecia

As mentioned before, the heterogeneity in clinical presentations—ranging from scarring to non-scarring alopecia—suggests the involvement of multiple pathogenic mechanisms. A pressure-induced mechanism, directly related to the infusion of mesotherapy solutions, has been proposed.[10] In cases of non-scarring alopecia, another plausible hypothesis involves direct cytotoxicity to hair follicle keratinocytes, potentially exacerbated by solvents like ethanol, used in the preparation. Ethanol has been implicated in follicular damage, potentially leading to hair loss without scarring due to suppression of metabolic activity and subsequent follicular miniaturization.[6] Ethanol is a common excipient in most mesotherapy solutions containing dutasteride. Conversely, scarring alopecia may result from a more intense inflammatory response, possibly due to hypersensitivity reactions or contamination, culminating in permanent follicular destruction and fibrosis. The variation in individual immune responses, injection techniques, and solvent compositions could further modulate these outcomes. These different mechanisms may coexist in the same patient and give rise to a continuous spectrum of changes between non-scarring and scarring forms, as exemplified by our second case. This variability also seems present in the remaining published cases, although limitations in those reports hinder the characterization of the underlying pathological process, such as the lack of information regarding the composition of mesotherapy solutions, absence of follow-up, and lack of trichoscopic descriptions and/or images in some of these cases.

It is also noteworthy that our cases occurred within a relatively narrow time frame. This temporal clustering suggests a shared extrinsic factor, such as an issue related to the specific lot used. Although no formal stability or contamination analysis of the preparation was conducted, this hypothesis cannot be excluded and may explain the unusual frequency and severity of the adverse events observed. Future cases should consider the importance of batch traceability and pharmacovigilance reporting when adverse outcomes arise in procedural dermatology.

Interestingly, distinct mechanisms may be involved in the development of paradoxical alopecia after mesotherapy. Al-Khalaf et al (2023) reported a female patient who developed pain and diffuse hair loss following mesotherapy, with trichoscopic findings consistent with alopecia areata.[8] The patient was treated with oral, intralesional, and topical corticosteroids, with partial improvement. Although it is difficult to establish a causal relationship, the authors discuss the possibility of mesotherapy-induced alopecia areata. Kadry et al (2008) also described a distinct case of scarring alopecia after mesotherapy in a young female patient who presented with scalp pain and draining abscesses, later yielding *Pseudomonas aeruginosa* and *Acinetobacter* on culture, and requiring intravenous antibiotic therapy and surgical drainage.[9] This case underscores the importance of strict aseptic technique to prevent post-procedural infection and subsequent secondary cicatricial alopecia.

This case series highlights the variability of clinical and trichoscopic findings in post-mesotherapy alopecia, ranging from permanent scarring to non-scarring alopecia, albeit with possible persistent miniaturization. Despite optimized medical management, aesthetic sequelae remained in all patients, some of whom ended up undergoing hair transplantation. Although there are few published cases to date, the authors note that similar occurrences remain unpublished, suggesting this may be an underrecognized phenomenon. These cases underscore the need for careful counseling regarding the potential risks of mesotherapy with dutasteride and for adequate follow-up after the procedure to detect complications early and prevent permanent sequelae.

DISCLOSURES

The authors have no conflicts of interest to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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doi:10.36849/JDD.9115

March 2026 256 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Pseudo-Psoriatic Nail Dystrophy Associated With Cosmetic Nail Products

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ABSTRACT

Pseudo-psoriatic nail dystrophy, a form of allergic contact dermatitis (ACD) secondary to nail product use, often mimics nail changes associated with psoriasis, leading to diagnostic delays. This review focuses on identifying dystrophic nail changes, particularly those resembling pseudo-psoriatic alterations, caused by cosmetic nail products and offers diagnostic and management strategies. Among the allergens listed as culprits, triethylene glycol dimethacrylate, hydroxyethyl acrylate, and hydroxyethyl methacrylate were the most common. This poses a challenge in differentiating between ACD and psoriatic onychodystrophy. Thus, enhanced diagnostic approaches emphasizing thorough history taking and appropriate patch testing recommendations are required. This study highlights the clinical overlap while emphasizing the absence of pathognomonic features like oil drops and salmon patches in PPND. Specialized patch testing for acrylates, often missing in standard panels, is crucial for accurate diagnosis. Findings show cessation of offending products significantly improves nail appearance within 3.5 months, reducing the need for systemic psoriasis treatments.

J Drugs Dermatol. 2026;25(3):256-262. doi:10.36849/JDD.9115

INTRODUCTION

Driven by the influence of social media, widespread availability of at-home nail kits, and easily accessible tutorials, the popularity of gel and acrylic nail polishes has surged making these stylish and long-lasting manicures more attainable than ever.[1,2] However, this increased accessibility has also raised the risk of overuse and improper application techniques, potentially leading to the development of allergic contact dermatitis (ACD) of the nails.[3] Both consumer populations and individuals working as nail artists and technicians have seen a notable increase in the incidence of this condition in recent years.[4] Data collected between 2009–2018 indicated a jump in the incidence of ACD due to acrylates found in nail products from 55% between 2009–2013 to 79% between 2014–2018.[5]

Due to suboptimal appearance and associated emotional distress, individuals may fall into a detrimental cycle of repeatedly applying various nail polishes to conceal damage, further exacerbating their condition. Patients seeking medical advice may present with severe nail damage, often a secondary result of allergic contact dermatitis, which can be mistaken for psoriatic nail dystrophy. This phenomenon is known as pseudo-psoriatic nail dystrophy (PPND).[6,7]

Clinicians may often find it challenging to distinguish between the clinical manifestations of ACD of the nail and psoriatic nail dystrophy, as ACD can also cause features classically associated with psoriatic nail dystrophy. These characteristics include subungual hyperkeratosis, generalized discoloration in yellow and brown hues, and onycholysis (Table 1).[8,9] Psoriatic nail changes commonly involve deep pitting, affecting approximately 68% of patients with psoriatic nail alterations.[10] The severity and duration of a patient's psoriasis correlate with the extent of nail pitting they experience, with the depth of these pits often indicating the duration of psoriasis flare-ups. Although pitting itself is not pathognomonic for psoriasis, clinicians can distinguish it from nail disorders like PPND by examining the depth and number of pits present across all affected nails. Other psoriatic nail changes include onycholysis, subungual hyperkeratosis, and discoloration described as "oil drops" or "salmon patches."[11,12] Notably, only oil drop/salmon patch discoloration is pathognomonic of psoriatic nail dystrophy, attributed to parakeratosis of psoriatic plaques on the nail bed.[10] Absence of this distinct discoloration may lead to misdiagnosis and inappropriate treatment, including confusion with ACD.

The primary allergens in gel nail polish often consist of methacrylates, as formaldehyde is now less commonly used.[13,14] Proper curing of gel polish with low-intensity UV light is crucial for acrylate polymerization, reducing the risk of an allergic response. However, incomplete curing may result in unpolymerized acrylates, substantially increasing the likelihood

TABLE 1.

Differentiating Between PPND Secondary to ACD and Psoriatic Nail Dystrophy		
Characteristic	**PPND Secondary to ACD**	**Psoriatic Nail Dystrophy**
Etiology	Secondary nail changes associated with ACD due to a specific allergen/irritant.	Autoimmune phenomenon associated with psoriasis. May present with other psoriatic disease manifestations such as joint involvement.
Nail Changes	Mimics psoriasis with possible: Nail pitting, Ridging Nail plate discoloration, Subungual hyperkeratosis, Splinter hemorrhages, Onycholysis, Periungual tissue damage, Fissured pulpitis Often isolated to nails without associated systemic involvement.	Typically presents with: Nail pitting, Ridging, Nail crumbling, Onychorrhexis, Subungual hyperkeratosis, Splinter hemorrhages, Onycholysis, Nail bed parakeratosis, Oil drops, Salmon patches, Leukonychia Dilation of capillaries of the proximal nail fold and thinning of suprapapillary plate best visualized on onychoscopy. Can affect nail bed, nail matrix, hyponychium, and nail folds.
Treatment	Patch testing to determine triggering allergen. Withdrawal and avoidance of potential allergen-containing products. +/- topical steroids.	Management of underlying systemic condition.

of ACD.[12,1] In this review, we aim to explore the various dystrophic and pseudo-psoriatic nail changes associated with allergens in cosmetic nail products and raise consumer awareness of such reactions. Furthermore, we aim to clarify the differences between onychodystrophy caused by nail products and psoriatic nail changes.

MATERIALS AND METHODS

Systematic Review

A systematic review of PubMed, OVID MedLine, CINAHL, and The Cochrane Library was conducted using PRISMA methods from database inception to December 10, 2023. Studies were identified through the following search phrases: "nail disease" or "psoriatic nails" in association with "nail polish", "nail cosmetics", and "dermatitis". Two investigators (BL and VS) independently screened titles and abstracts that documented the presence of cosmetic nail product use and associated nail changes. Any conflicts were resolved by a third reviewer (AH).

Inclusion and Exclusion Criteria

The inclusion criteria for the study were research articles that specifically mentioned the correlation between psoriatic nails or nail diseases with the use of nail polish, nail cosmetics, or dermatitis. Studies examining the relationship between cosmetic nail product usage and associated nail changes were included. Additionally, articles focusing on psoriatic nails in conjunction with other relevant terms such as nail lacquer, nail varnish, or nail care products were considered for inclusion.

Exclusion criteria were articles that referenced skin conditions unrelated to nail diseases or psoriatic nails, such as general skin irritations, allergic reactions not directly associated with the use of nail cosmetics, or unrelated dermatological conditions such as onychomycosis and paronychia. Furthermore, studies emphasizing mechanical nail damage without a direct link to nail cosmetics or psoriatic nails were excluded.

Relevant demographic data from applicable studies were collected, including information regarding the patients' sex, age, type of cosmetic nail product exposure, duration of exposure, timing, and duration of nail dystrophy and clinical presentations. When available, patch testing results, clinically relevant allergens, treatment plans, and outcomes were also recorded.

RESULTS

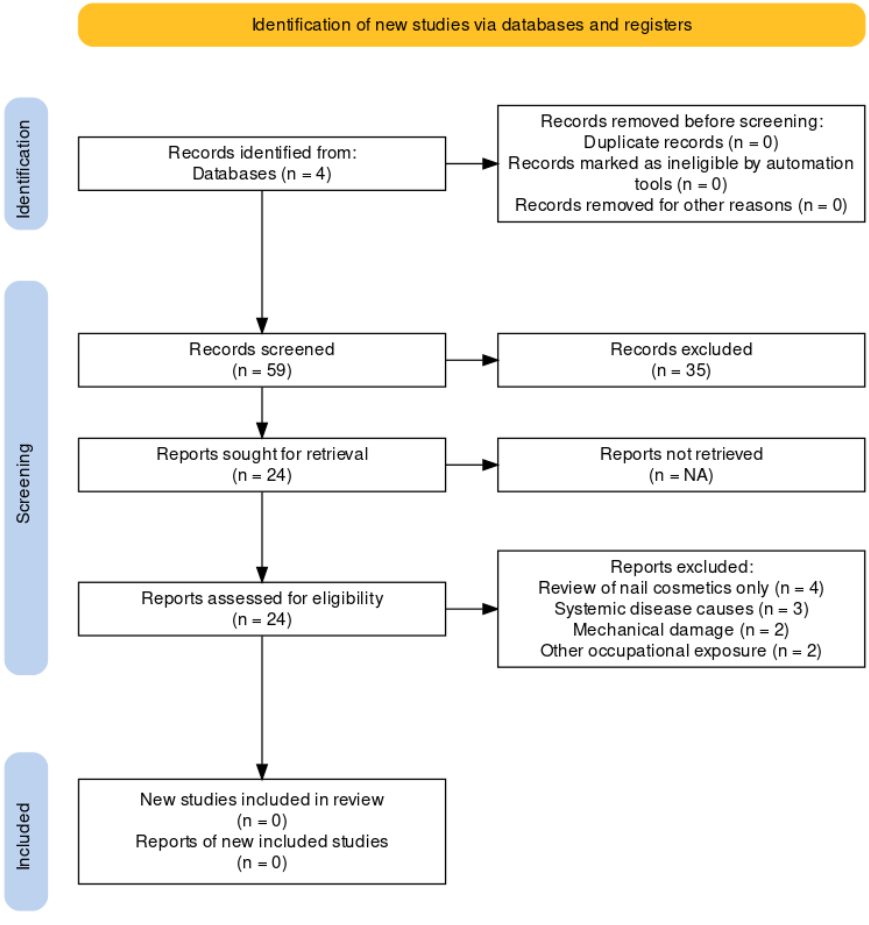
Literature Search

A total of 59 articles were retrieved, with 13 records meeting the inclusion criteria (Figure 1). Within these, 15 patient cases were documented, each presenting evidence linking various nail varnishes to pseudo-psoriatic nail changes. Among the 15 cases, 60% were associated with gel nail polish or acrylic nails, while the remaining 40% were linked to nail hardener, nail glue, or other unspecified nail products.

Patient Demographics

Of the 15 cases that met the inclusion criteria, 100% involved female patients of an average age of 47 years (range, 30–61 years; Table 2). Three patients reported that their occupation was in a nail salon, either as a technician or as a receptionist. The average duration of nail changes across all cases was 9.3 months (range, 3 weeks to 4 years). The most common

FIGURE 1. PRISMA diagram of search strategy.



Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing P*RISMA* 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst Rev.* 2022;18(2):e1230

FIGURE 2. Allergen prevalence on patch testing in reported cases.

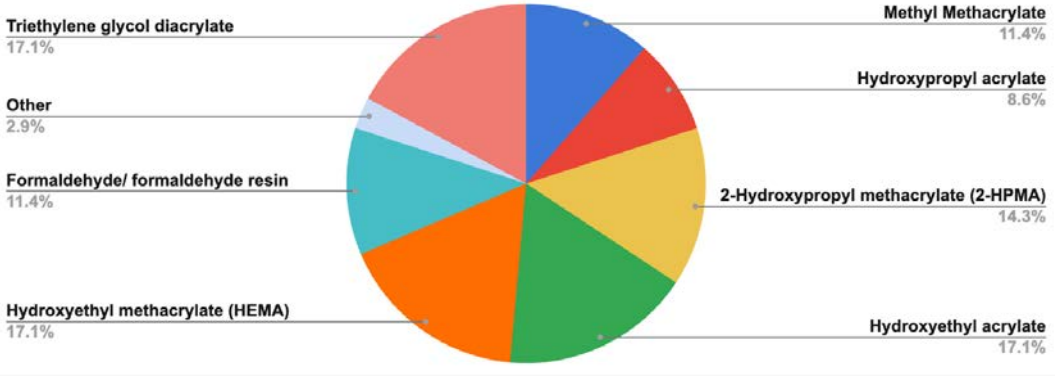


TABLE 2.

Reported Cases of Nail Dystrophy With Permanent Nail Polish Use

Reference	Age (Years)	Duration of nail changes	Nail Findings	Exposure	Positivity on Patch Testing		Outcome
Coe et al	60	4 years	Fingernail dystrophy	Gel polish, nail glue, nail lacquers; worked as receptionist at nail salon.	2-Hydroxyethyl methacrylate Methyl methacrylate 2-Hydroxypropyl methacrylate Ethyleneglycol dimethacrylate Triethyleneglycol dimethacrylate 1,4-Butanediol diacrylate Urethane methacrylate 1,6-Hexanediol diacrylate Tetrahydrofurfuryl methacrylate Tetraethylene glycol dimethacrylate	N-butyl acrylate Ethyl methacrylate Ethyl acrylate 2-Hydroxyethyl acrylate Triethylene glycol diacrylate Isobornyl acrylate Ethyl cyanoacrylate Tosylamide formaldehyde resin Adipic acid/neopentyl glycol/ trimellitic anhydride copolymer Phthalic anhydride/trimellitic anhydride/glycols copolymer	Initially diagnosed with psoriasis and treated with ILK, PUVA, acitretin, MTX, apremilast, adalimumab without improvement. After two months of discontinuing all nail products, patient noted significant improvement.
Lahouel et al	38	4 months	Localized subungual hyperkeratosis, subungual thickening, fissured pulpits	Acrylic, gel, and glue-on nails; worked for 10 years as a nail technician.	2-hydroxyethyl methacrylates		Improvement noted 2 months after discontinuation of all nail products.
Shim et al	30	2 years	Onycholysis, oil spots	Acrylic and gel polish over several years.	Methyl methacrylate Diethylene glycol diacrylate	Ethyl acrylate Hydroxypropyl acrylate	Treated with oral antifungal, topical vitamin D analogues, and topical steroids with no improvement. Significant improvement after 3-6 months of complete nail product discontinuation.
	45	Not documented	Brittle, discolored fingernails, generalized onycholysis, toenail subungual hyperkeratosis	Gel nail product use for over 20 years.	Hydroxyethyl methacrylate Ethyl acrylate Butyl acrylate 2-hydroxyethyl acrylate, Hydroxypropyl acrylate Methyl methacrylate	Ethyl methacrylate 2-hydroxypropyl methacrylate Ethylene glycol dimethacrylate 1,4-butanediol diacrylate Diethylene glycol diacrylate Triethylene glycol diacrylate	Significant improvement after 3-6 months of complete nail product discontinuation.
	38	1 year	Discolouration, splinter hemorrhages, onycholysis	Acrylic and gel nail polish.	Hydroxyethyl methacrylate Ethyl acrylate 2-hydroxyethyl acrylate Hydroxypropyl acrylate 2-hydroxypropyl methacrylate Ethylene glycol dimethacrylate	Diethylene glycol diacrylate Triethylene glycol diacrylate Triethylene glycol dimethacrylate 1,4-butanediol dimethacrylate Urethane dimethacrylate 1,4-butanediol acrylate	Significant improvement after 3-6 months of complete nail product discontinuation.
Mendoca et al	51	2 months	Onycholysis, subungual hyperkeratosis, post-inflammatory, brown pigmentation of proximal nail folds.	Acrylic nail application for 6 years.	Patch testing not performed		Not documented.
	59	Not documented	Subungual hyperkeratosis and onycholysis	Gel polish.	Methyl methacrylate 2% pet	Toluenesulphonamide formaldehyde resin 10% pet	Treated with acitretin and cyclosporine for nail psoriasis with no improvement. Improvement seen after 45 days of complete avoidance of nail products and weekly topical steroids.
Guin et al	38	2 months	Nail lifting, onycholysis	Permanent nail polish without curing with UV/LED	2-ethylcyanoacrylate		Improvement with nail growth.
Cousen et al	49	3 months	Subungual hyperkeratosis, periungual erythema, proximal nail fold pain	Gel polish application every 3 weeks.	Ethylene glycol dimethacrylate Triethyleneglycol dimethacrylate Urethane dimethacrylate Hydroxyethyl methacrylate	Butyl methacrylate 2-hydroxypropyl methacrylate Ethyl acrylate Hydroxyethyl acrylate Triethylene glycol diacrylate	Not documented.

TABLE 2. (CONTINUED)

Reported Cases of Nail Dystrophy With Permanent Nail Polish Use						
Reference	Age (Years)	Duration of nail changes	Nail Findings	Exposure	Positivity on Patch Testing	Outcome
Helsing et al	59	3 weeks	Onycholysis, pain, subungual hemorrhage, nail plate discoloration, anonychia of 3 nails.	Nail hardener	Formaldehyde 1% Quaternium-15 1%	Improved 8 months after nail product discontinuation.
Adigun et al	43	7 months	Distal onycholysis, splinter hemorrhages, notable plate thinning, subungual hyperkeratosis	Acrylic and gel polish use.	Patch testing not performed	Oral terbinafine, topical efinaconazole 10%, and oral itraconazole for 3 months with no improvement. Intralesional triamcinolone 10mg/cc to all 20 digits repeated every six weeks for six months; topical clobetasol 0.05% ointment BID with significant improvement.
Mestach et al	49	Not documented	Nail discoloration, anonychia.	Nail hardener	Formaldehyde 2% aq. Quaternium-15 Imidazolidinyl urea Diazolidinyl urea DMDM hydantoin Fragrance mix I Linalool hyperperoxides Tosylamide/formaldehyde resin Disodiym tetrachloropalladinate 3%	Not documented.
Piraccini et al	51	6 months	Mild onycholysis surrounded by an erythematous border and subungual hyperkeratosis	Artificial nail use for 6 years.	Paraphenylenediamine Diethyleneglycol diacrylate, Triethyleneglycol diacrylate Ethylene glycol dimethacrylate 2-hydroxyethyl methacrylate 2-hydroxypropyl methacrylate	Diagnosed with psoriasiform acral dermatitis.
Foti et al	37	1 month	Paronychia, onycholysis, onychodystrophy of all fingernails	Pre-formed acrylic nails and nail glue for 3 months.	Nickel sulfate	Discontinuation of artificial nails resulted in gradual improvement and residual onychorrhexis after 6 months.
Hwang et al	61	3 months	Yellowish chromonychia; pincer nail deformity of both thumbnails, nail pitting, pseudo-leukonychia, trachyonychia.	Gel polish application weekly for 5 months.	Patch testing not performed	Improvement after 6 months with nail grinding.

morphologies besides nail dystrophy included onycholysis (66.7%), subungual hyperkeratosis (60%), and discoloration (40%). 33% of reported cases also reported a prior misdiagnosis of psoriasis or onychomycosis.

Patch Testing and Outcomes

Patch testing results were available for 12 of the 15 cases, revealing 64 clinically-relevant positive reactions to various allergens (Figure 2). Notably, acrylates in various forms were present in 72.7% of the cases. Among the allergens, triethylene glycol dimethacrylate, hydroxyethyl acrylate, and hydroxyethyl methacrylate (HEMA) were the most common allergens, each of which was present in 17.1% of cases, followed by 2-hydroxypropyl methacrylate (2-HPMA) at 14.3%. Less common allergens were formaldehyde (11.4%), methyl methacrylate (11.4%), and hydroxypropyl acrylate (8.6%). Of the cases that provided proper treatment of complete cessation of all nail products, patients noted improvement in the appearance of nails in an average of 3.5 months (range, 1.5–6 months).

DISCUSSION

While acrylates in nail polish products are widely recognized culprits in causing ACD, hand and finger dermatitis is the most common presentation.[2] Patients will often seek medical care when the reaction involves the nails themselves, resulting in an aesthetically displeasing appearance. In reported cases of nail dystrophy associated with cosmetic nail products, various forms of acrylates, notably triethylene glycol dimethacrylate, HEMA, and hydroxyethyl acrylate, have emerged as the most common allergens.[6] These components are essential in the formulation of many gel nail polishes, primers, and bonders.

The allergenic potential of these compounds primarily stems from their capacity to undergo an exothermic polymerization

reaction when exposed to UV light during the process of curing gel nail polish.[1] Polymerization entails the formation of long chains of molecules, allowing for the resins to harden and firmly adhere to the nail surface.[1] However, if these gel polishes are inadequately cured or if residual uncured acrylates come in contact with the skin, a sensitization reaction may occur, resulting in dermatitis of the skin or nail.

Significant nail changes manifested at varying times among reported cases, with some instances revealing undesirable reactions within a week of product use, while others appeared years after recurrent gel or acrylic nail polish application.[8] Besides generalized dermatitis of the hands, patients frequently exhibited onychodystrophy, onycholysis, paronychia, and subungual hyperkeratosis.[8] These clinical manifestations can closely resemble psoriatic changes, underscoring the importance of obtaining a comprehensive medical history and thorough physical examination whenever possible.

When seeking to perform patch testing for patients with PPND, physicians should be mindful of the allergen panel being tested; for example, triethylene glycol dimethacrylate is not found on the NAC-80. Since many of the noted allergens are frequently found in dental adhesives and other dental restorative materials, they can be tested for using a combination of the (Meth) Acrylate Series for Adhesives, Dental, Printing and Other Methacrylates and (Meth) Acrylate Nail Series developed by Chemotechnique Diagnostics® (Vellinge, Sweden).[15] Specialized patch testing panels can also be obtained from SmartPractice Allergen Bank Pharmacy (Arizona, USA), an online resource that allows for customization and testing of more obscure allergens.

Prior to initiating biologic medications for suspected psoriatic nail disease, patch testing should be considered first to rule out PPND in certain patients. Patch testing to identify ACD may also help to avoid unnecessary treatment and prevent potential adverse side effects associated with systemic therapies. This method may facilitate cost-conscious care and reduce the need for expensive, unnecessary therapies. This model may also reduce administrative burden: biologic drugs require prior authorizations greater than 95% of the time, with approximately 17% of prior authorization determinations taking longer than two weeks to process, potentially prolonging a patient's exposure to triggering allergens.1[6] Additionally, patients with recurrent/chronic ACD who received relevant positive results on patch-testing were shown to have significant improvement in symptom severity and quality of life measures 2 months after testing.[17]

If relevant allergens are determined, dermatologists should provide counseling on exposure avoidance, as well as relevant occupational health counseling for patients working in the nail cosmetics industry. Both consumers and industry professionals should actively seek safer formulations and nail products that avoid common allergens, including triethylene glycol dimethacrylate, HEMA, and HPMA when possible. If individuals prefer gel polishes over traditional nail lacquers due to their durability and luster, emphasis should be placed on the importance of proper curing. Allowing adequate time for complete polymerization during curing can reduce the incidence of such reactions.[1] Furthermore, individuals can initially trial polishes on a single nail to assess for potential short-term allergic reactions, in a manner similar to the reactive open activation test (ROAT).

Nail technicians should also receive counseling regarding proper protection measures while working on other clients' nails, including utilizing nitrile gloves or 4H gloves when able. While 4H gloves offer the greatest level of protection against acrylate permeation, they can be bulky and impair dexterity.[13] By contrast, certain nitrile gloves have demonstrated efficacy in halting acrylate permeability and elicitation of positive patch test reactions for up to one hour.[13] In addition, nail technicians should wear protective eyewear and masks to prevent inadvertent exposure to polymer particles, which could lead to sensitization and development of ACD in other areas of the face and body.

CONCLUSION

PPND should be considered in the differential diagnosis for patients who have been exposed to nail cosmetic products and present with nail changes resembling those of psoriasis. Hallmarks of psoriatic nail dystrophy, such as the presence of oil drops, patch discoloration, and parakeratosis of the nail bed, may help distinguish between psoriatic nail dystrophy and nail changes resulting from allergic contact dermatitis. Furthermore, for patients with relevant exposure history, dermatologists should prioritize patch testing and consider specialized panels for acrylate allergy to rule out ACD prior to initiating systemic psoriasis treatments.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.9496

March 2026 263 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Management of Nail Toxicities From Fibroblast Growth Factor Receptor Inhibitors

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ABSTRACT

Background: Alterations in fibroblast growth factor receptor (FGFR) signaling are present in many malignancies, including urothelial carcinoma, cholangiocarcinoma, and gastrointestinal cancers, and FGFR inhibitors (FGFRi) play an increasing role in the treatment of these malignancies. Nail toxicities, such as onycholysis, paronychia, and nail fragility are an important part of the adverse effect profile of FGFRi that remain underrecognized and poorly characterized.

Methods: We conducted a systematic literature review using PubMed and Google through March 2025, including case reports, trials, and retrospective studies reporting FGFRi-related nail disorders. Search terms included individual FGFRi (e.g., erdafitinib, pemigatinib, futibatinib) and nail-related adverse events. Data on incidence, severity (CTCAE v5.0), onset, management, and treatment impact were extracted. Statistical analyses included the Wilcoxon and Chi-square tests.

Results: Twenty-three studies with 1,561 patients were analyzed. Out of these, 540 patients experienced nail toxicity. Erdafitinib had the highest nail toxicity rate (43.3%) and derazantinib the lowest (5.3%). Grade 1–2 events were most common; Grade 3 events prompted dose reduction in three patients out of 540, though no treatment discontinuations were reported. Common management strategies included antiseptic soaks, topical steroids, oral antibiotics, and protective nail care practices.

Discussion/Conclusion: The incidence of FGFRi-associated nail toxicities varies by agent and can affect quality of life and treatment adherence. The pathogenesis remains unclear, and no predictive biomarkers exist. Further research into optimized management and preventative strategies is needed. Early recognition and proactive multidisciplinary management are essential to minimizing complications and maintaining oncologic treatment continuity.

J Drugs Dermatol. 2026;25(3):263-267. doi:10.36849/JDD.9496

INTRODUCTION

Fibroblast growth factor receptor inhibitors (FGFRi) are a novel class of targeted therapies used in the treatment of FGFR-mutant malignancies. Aberrant FGFR signaling via gene amplification, overexpression, activating mutations, or gene fusions is implicated in a variety of cancers, including breast, gynecological, urothelial, hematopoietic, and gastrointestinal malignancies.[1] In this study, we focused on the current FDA-approved selective FGFRi which include pemigatinib, futibatinib, and erdafitinib along with new FGFRi that are currently under clinical trials.[2,3]

While dermatologic toxicities such as acneiform dermatitis, xerosis, and mucositis are well-recognized adverse effects of many targeted oncologic therapies, FGFRi have a unique propensity to cause nail toxicities that may be less familiar to the oncologist or general dermatologist. FGFR signaling is important for cellular homeostasis of the nail unit, and blocking this pathway can lead to nail dystrophy, fragility, detachment, or inflammation.[4] While FGFR1 and FGFR2 primarily regulate epithelial and mesenchymal tissues such as skin and nails, direct evidence linking nail toxicities to inhibition of specific FGFR complexes remains limited.

There remains a lack of comprehensive literature focused specifically on the clinical characteristics, incidence, and management of FGFR inhibitor-related nail toxicities. Most available data on FGFRi-associated nail disorders are limited to isolated case reports or brief mentions within broader studies of cutaneous adverse events of these drugs. This has led to underrecognition of these findings in both clinical practice and clinical trial reporting. Given the growing use of FGFRi across multiple malignancies and the role nail disorders can play in negatively impacting patient quality of life, there is a clear need for a consolidated review of current knowledge. Therefore, we conducted this systematic review to compile and analyze all available evidence on FGFRi-associated nail toxicity, to improve recognition, facilitate earlier intervention, and guide future research efforts in this area.

MATERIALS AND METHODS

A systematic literature search was conducted using PubMed and Google. Keywords included "FGFR inhibitor," along with the individual medications under this class, including erdafitinib, pemigatinib, futibatinib, infigratinib, and derazantinib. Specific terms for nail toxicities used in the search included nail, nail changes, onycholysis, brittle nails, onychodystrophy, Beau's

lines, nail fragility, paronychia, subungual hemorrhage, and subungual abscess.

Clinical trials, case series, case reports, and retrospective studies published in English until March 2025 and reporting nail-related adverse events and patient outcomes on FGFR inhibitors were included. Data on incidence, severity, time to onset, management, and impact on therapy adherence were extracted. The severity of nail toxicity was graded (Table 1) using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) reporting guidelines.[5]

Analysis was performed on SAS software and involved Wilcoxon and Kruskal-Wallis tests for continuous variables and Chi-square test for categorical variables.

RESULTS

Twenty-three studies (reference 6-29) published from 2015 to 2025, consisting of a total of 1,561 patients were included in the study. The largest patient cohorts were those receiving futibatinib (639, 40.9%) and pemigatinib (401, 25.7%).

Among the largest patient cohorts, nail toxicity was most frequently observed in individuals treated with erdafitinib or pemigatinib. In our pooled analysis, pemigatinib was associated with nail toxicity in 170 of 401 patients (42.4%), whereas futibatinib demonstrated a lower incidence (189 of 639 patients, 29.6%).

The incidence of nail toxicity differed significantly across FGFRi (P<0.0001), with the proportion of affected patients ranging

TABLE 1.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grading Scale of Nail Unit Toxicities, Adapted From the National Cancer Institute (NCI)

Adverse Event	Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.	Grade 4: Life-threatening consequences: urgent intervention indicated.	Grade 5: Death related to Adverse Event.
Nail changes	Present	--	--	--	--
Nail discoloration	Asymptomatic; clinical or diagnostic observations only	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental activities of daily living	--	--	--
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental activities of daily living	--	--	--
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	--	--	--	--
Nail infection	Localized, local intervention indicated	Oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	--	--
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental activities of daily living	Operative intervention indicated; IV antibiotics indicated; limiting self-care activities of daily living	--	--

TABLE 2.

Summary of Nail Toxicities Associated with FGFR Inhibitors (Aggregated by Drug)

Drug	Total Patients (n)	Patients With Any Nail Toxicity, n (%)	Grade 1-2, n (%)	Grade ≥ 3, n (%)
Futibatinib	639	189 (29.6%)	184 (28.8%)	5 (0.8%)
Pemigatinib	401	170 (42.4%)	159 (39.7%)	11 (2.7%)
Erdafitinib	298	129 (43.3%)	91 (30.5%)	38 (12.8%)
Infigratinib	62	31 (50.0%)	30 (48.4%)	1 (1.6%)
Fexagratinib*	14	10 (71.4%)	9 (64.3%)	1 (7.1%)
Derazantinib*	132	7 (5.3%)	7 (5.3%)	0 (0.0%)
Rogaratinib*	15	4 (26.7%)	2 (13.3%)	2 (13.3%)
Total	1561	540	482	58

*These therapies have not yet received FDA approval and are being evaluated in ongoing clinical studies.

TABLE 3.

Commonly Reported Strategies for Various Nail Events as per Systematic Review

Nail Concern	Type of Strategy	Management Strategy
Grade 1 nail event induced by FGFRi	Topical	Moisturizers, steroid creams
Grade 1-2 nail event induced by FGFRi	Topical, oral and supportive	Daily antiseptic soak, metronidazole cream to nail, doxycycline
Grade 1-2 nail event induced by FGFRi	Topical	Silver nitrate application weekly, and topical antibiotics and vinegar soaks
Infection	Topical and oral	Oral antibiotics (cefadroxil 500 mg twice daily, ciprofloxacin 500 mg twice daily, or sulfamethoxazole/trimethoprim twice daily) for 2 weeks

from 5.3% for derazantinib to 71.4% for fexagratinib. Erdafitinib exhibited the highest proportion of grade ≥3 nail toxicities (38 of 298 patients; 12.8%), whereas futibatinib and derazantinib demonstrated low rates of high-grade nail events (≤1%).

When categorized by severity, most FGFRi were associated with grade 1–2 nail toxicities, occurring in approximately 28–40% of treated patients, with higher rates observed for agents such as fexagratinib in smaller cohorts. Grade ≥3 nail events were observed less frequently, generally in <5% of cases, although erdafitinib demonstrated a notably higher rate (12.8%). Non-parametric testing (Wilcoxon and Kruskal–Wallis) demonstrated a statistically significant difference in nail toxicity severity across FGFR inhibitors (P<0.0001), highlighting marked variability between agents. When grade 2–3 nail events occurred, dose reduction of the FGFR inhibitor was considered; in total, three patients underwent dose modification due to nail toxicity, and no treatment discontinuations were reported in this dataset. Common management strategies for FGFRi-associated nail toxicities identified through our systematic review are shown in Table 3.

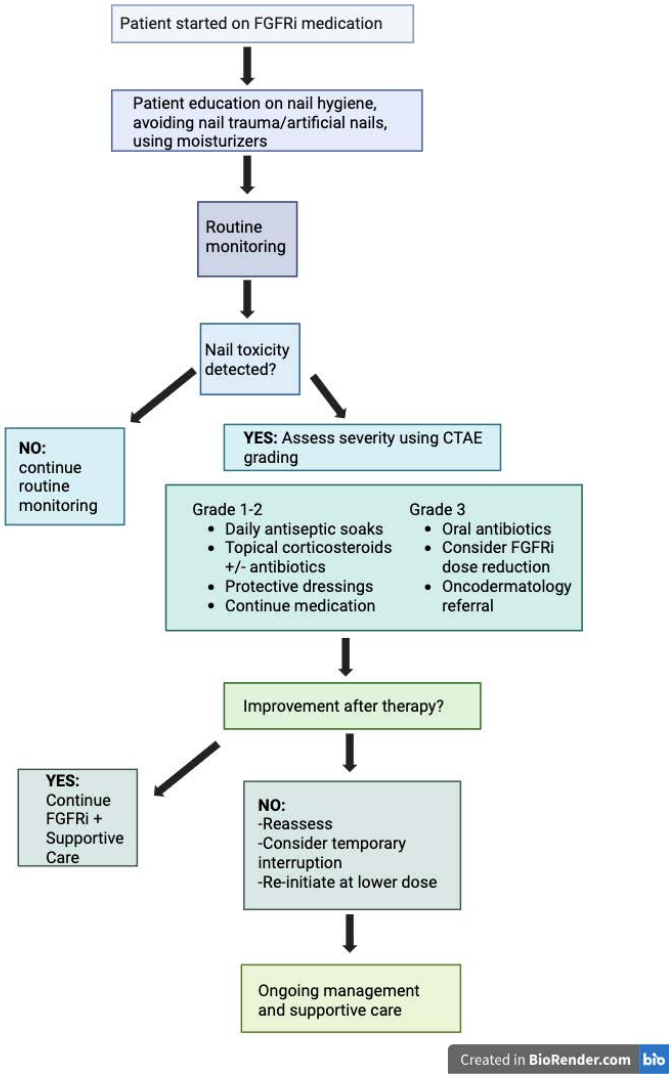
DISCUSSION

This systematic review highlights the marked variability in the incidence, severity, and clinical spectrum of nail toxicities across FGFR inhibitors. In our pooled analysis, erdafitinib demonstrated the highest overall incidence of nail toxicity (129 of 298 patients; 43.3%), whereas derazantinib showed the lowest rate (7 of 132 patients; 5.3%). Although most agents were associated predominantly with low-grade (grade 1–2) nail toxicities, the proportion of high-grade (grade ≥3) events differed substantially; notably, erdafitinib exhibited the highest rate of severe events (12.8%), whereas futibatinib and derazantinib had very low rates (≤1%). The statistically significant differences in nail toxicity severity (P<0.0001) across FGFR inhibitors suggest that certain agents may require more proactive supportive care strategies and earlier dose modification to maintain treatment adherence. These findings underscore the importance of early recognition and tailored management of FGFRi-associated nail toxicities, particularly for agents with higher rates of severe events, as summarized in Figure 1 below.

Once an FGFR medication has been started, the development of nail toxicities has a median time to development of about 1–2 months. These toxicities are progressive, can significantly impact patients' quality of life, and may lead to dose reductions or treatment interruptions. Early referral to a dermatologist specializing in cutaneous toxicities of oncologic therapy may help in early diagnosis, symptom management, and prevention of superinfection or other complications.

Multiple interventions have been recommended for nail toxicities of FGFR inhibitors. Preventative strategies include meticulous nail trimming (avoidance of trimming the distal nail edge too closely or leaving it too long), consistent moisturization of the cuticle, and avoidance of artificial nails, which may obscure early signs of infection and promote secondary complications.[2]

FIGURE 1. Flowchart of management of FGFRi-induced nail toxicities.[30,31]



In cases of drug-induced onycholysis, particularly those linked to FGFRi, meticulous nail care is again essential to prevent secondary infection and minimize the risk of permanent dystrophy. The onycholytic portion of the nail plate should be carefully trimmed rather than manually lifted, as lifting may exacerbate separation.The exposed nail bed should be cleansed with daily antiseptic soaks; however, povidone-iodine should be avoided due to its drying effect on surrounding skin.

For significant inflammation or suspected superinfection, topical antibiotic–corticosteroid combinations may be beneficial. Preparations containing gentamicin should be avoided due to their sensitization potential; preferred alternatives include fusidic acid or mupirocin. If the nail bed is extensively exposed, coverage with non-adherent, moistened gauze can help preserve the moist environment necessary for healing.[4,7]

Patients should be counseled on preventive nail care and early symptom reporting. Gloves are recommended for household or gardening tasks. Nail-strengthening products and artificial nails should be avoided, as they may cause irritation or mask signs of nail damage. Any pain, redness, or swelling around the nails or cuticles should be promptly reported. In suspected infections, bacterial cultures should be obtained, empiric antibiotics initiated, and dermatology referral considered.[3,4]

Close monitoring is necessary to detect evolving nail dystrophy or permanent onycholysis, particularly when epithelialization of the exposed nail bed may impede regrowth. Although nail fragility and onycholysis are increasingly reported, the underlying pathogenesis remains unclear.[31] It is suspected that FGFR inhibition disrupts nail matrix keratinocyte function, with potential vascular or inflammatory contributions. Currently, there are no predictive markers to identify patients at risk for nail toxicity. Long-term outcomes remain uncertain, especially regarding the reversibility of these changes and the risk of permanent dystrophy. Future strategies to mitigate FGFRi-induced nail toxicities may include topical agents that protect against keratinocyte injury or development of novel FGFR inhibitors selective for visceral rather than cutaneous receptor subtypes.

This study is limited by its retrospective design, uneven subgroup sizes across agents, and lack of standardized treatment protocols. Additionally, the absence of long-term follow-up limits understanding of the chronicity and reversibility of FGFRi–associated nail changes. As FGFRi are increasingly used, adverse nail events should be anticipated and addressed early. Future research should focus on prospective studies to identify predictive biomarkers for severe nail toxicity. Multidisciplinary collaboration among oncologists, dermatologists, and supportive care specialists will be essential for developing standardized management guidelines. We advocate for increased awareness, early intervention, and further research to refine treatment strategies and improve the quality of life for patients receiving FGFR inhibitors.

DISCLOSURES

The authors have no conflicts of interest to report.

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doi:10.36849/JDD.9677

March 2026 268 Volume 25 • Issue 3

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Transitioning From Anti-aging to Skin Activation: Limiting Cellular Fatigue and Senescence for Skin Longevity

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ABSTRACT

Background: Skin thinning, known as dermatoporosis, is an expected consequence of aging that involves structural weaknesses, barrier deficiencies, and cellular senescence, posing challenges for maintaining long-term skin health.

Objective: To introduce Skin Activation as a dermatologic strategy for promoting skin longevity. It is supported by clinical and preclinical evidence, combining methods to remodel the extracellular matrix (ECM) and dermo-epidermal junction (DEJ), restore the barrier, and enhance hydration, along with reducing senescent cells. This improves the skin's functional resilience.

Methods: Data were generated from a multicenter dermatoporosis trial, a randomized controlled trial, and specific cohorts of sensitive skin patients, in addition to preclinical studies. Study endpoints included trans-epidermal water loss (TEWL), hydration levels, LC-Optical Coherence Tomography (LC-OCT), assessments of the DEJ, ultrasound measurements, senescent markers, and histology. The data also included measures of senescence, cytokine profiles, and biomarkers of cellular renewal.

Results: Among 400 participants, notable changes included a 20-40% reduction in TEWL, an 80% increase in hydration based on corneometer readings, a 5% rise in skin thickness, and improved DEJ integrity in 83% of subjects compared to 17% of controls. In preclinical ex vivo models, decreases in fibroblast senescence levels were observed, along with activation of the JAG/NOTCH pathway.

Conclusion: A recently developed skin activator program shifts dermatologic skin health strategies from a broad anti-aging focus to a more targeted skin activation approach focused on structure, function, and cellular energy and renewal. This reinforces the ongoing commitment to dermatological innovation and establishes a more structured approach to skin longevity.

J Drugs Dermatol. 2026;25(3):268-272. doi:10.36849/JDD.9677

INTRODUCTION

The concept of 'anti-aging' has been openly used for many years to describe a wide range of changes, from smoothing fine lines and wrinkles to improving hydration and pigmentation. This terminology is gradually being replaced by a new term, longevity, which is also very broad and often difficult to interpret. Of course, these factors matter to patients, but the underlying biological processes we've identified over the past two decades—related to a decline in skin health and resilience—are not well represented. These biological processes affecting skin longevity and resilience include ECM degradation, fragmentation and collapse, DEJ effacement and flattening, barrier protection dysfunction, loss of cellular energy and mitochondrial function, increased reactive oxygen species (ROS), and the eventual buildup of senescent cells along with chronic 'inflammaging'. In large part, these changes occur as cells grow weary and become less active due to the buildup of these ROS and other degenerative intrinsic and extrinsic factors.

The hallmarks of aging, initially defined in 2013 by López-Otín[1] et al and later refined in 2023,[2] establish a biological framework for cellular aging that includes, among others, genomic instability, mitochondrial dysfunction, telomere attrition, epigenetic changes, altered autophagic response, and stem cell exhaustion. These factors are especially relevant to the skin, representing cellular exhaustion that manifests in skin aging and decreased longevity.

It is essential to understand that the term 'skin longevity' should not be confused with the concept of lifespan extension related to chronological age, where significant efforts and large financial investments are made to increase overall lifespan with limited tangible results so far. Skin longevity, or more accurately, skin activation, based on the biological processes mentioned above, has seen considerable progress in recent years. Our experience in this area is shared here. An additional semantic point worth noting is that we have deliberately described the

program as a 'skin longevity' program rather than a 'cellular longevity' program. As skin ages, cellular turnover decreases. In youth and adolescence, cells turn over every 10-20 days; this slows with age to around 60 days. In other words, our goal is not to prolong cell life, but to have healthy, energized cells with optimized turnover rates that result in healthy, resilient skin. To reflect this, we have established a more functional descriptor with our 'skin activator program,' which describes the re-energizing of worn-out cells, positioning it within the skin longevity field but with a more targeted approach. A recent publication has used the term 'skinspan' for skin longevity,[3] but in both cases, the implication is that we are trying to make skin survive longer. Skin activation still falls under the definition of skin longevity but emphasizes that we are re-energizing or re-activating worn-out cells, which is at the heart of our strategy to improve skin resilience.

Dermatoporosis (DP), first identified by Kaya and Saurat in 2007, is a condition characterized by skin aging marked by progressive thinning, increased fragility, skin tears, and bruising.[4] Although this represents the advanced stage, it can be compared to the 'osteoporosis' of the skin, indicating it begins early, is widespread, and affects nearly the entire population. The most effective management approach is likely preventive—delaying its onset and addressing the underlying processes that contribute to its development. What better condition could exemplify skin's longevity and resilience? We have chosen to use this condition as a symbol of skin activation, highlighting our efforts to reverse or delay its progression across different age groups with various formulations from our portfolio. This demonstrates why dermatoporosis is considered the 'poster child' for studying cellular deactivation and skin longevity.

This review of strategy and results introduces 'skin activation' as a descriptive and intervention-focused paradigm that extends beyond cosmetic anti-aging. We define skin activation, which promotes skin longevity, as the preservation of youthful traits in young people and the restoration of these features in older populations. This involves maintaining structural integrity (ECM, DEJ), supporting barrier health (reducing TEWL, increasing hydration, stimulating basement membrane proteins with peptides), and enhancing cellular energy and vitality (limiting senescence, improving mitochondrial function). As an evidence-based approach, this combines data from clinical trials, multicenter studies, and preclinical research using ex-vivo models, establishing skin activation as a measurable concept rooted in scientific evidence and providing a foundation for dermatologic innovations and treatments. We demonstrate that the lost activation potential of aging skin and its regenerative capacity can be reignited with a targeted activation intervention.

MATERIALS AND METHODS

This paper synthesizes and integrates findings from:

- A double-blind randomized controlled study comparing TriHex technology with a ceramide cream in dermatoporotic patients' arms—using ultrasound, LC-OCT, histology, and clinical end-points.[5]
- A dermatoporosis study in patients aged 65-82 years old, focusing on sensitive skin and photodamage in older individuals, assessing TEWL, hydration, ultrasound, and skin thickness.[6]
- A dermatoporosis study in patients aged 40-75 years (including those with sensitive skin and photodamage at younger ages), assessing tolerability, pinch recoil resilience, and clinical density.[7]
- Strategies for restoring the ECM in dermatoporosis using TriHex technology, ECM remodeling, and reversing fibroblast senescence.[8]
- Preclinical study on strengthening dermatoporotic skin by reducing cellular senescence using Cetaphil activator cream formulation. Assays conducted on fibroblasts, keratinocytes, and full ex-vivo models treated with micro-dosed Centella asiatica and mandelic acid, measuring senescent cell responses, cytokine expression, and regenerative signaling (JAG/NOTCH).[9]
- TriHex technology and anti-aging skin biomarkers assessing telomere length, KLOTHO, FGF23, FGFR1and FOXO3B anti-aging gene biomarkers.[10]

RESULTS

For clarity, results will be reported according to the biological processes outlined above in the 'skin longevity' program – thus:

ECM and DEJ Remodeling – Structural Changes

In the double-blind randomized clinical trial, TriHex technology (ReFORM & RePAIR with TriHex® Technology, Alastin Skincare, Inc., Carlsbad, CA, a Galderma company, USA) significantly outperformed the ceramide control formulation. Specifically, LC-OCT and ultrasound revealed a reversal of effacement, along with the restoration of a strengthened DEJ and rete peg undulation. Notably, 83% of subjects treated with TriHex showed changes in undulation, compared to 17% in the control group[5] (Figure 1). This finding prompted further investigation into early signs of DP reversal, first indicated by changes observed at the DEJ (paper in submission JDD). DEJ histology confirmed ECM

FIGURE 1. Ultrasound image showing baseline (left) versus Alastin R&R-treated arm (right), with increased thickness and reconstitution of the DEJ (blue band) after 24 weeks.

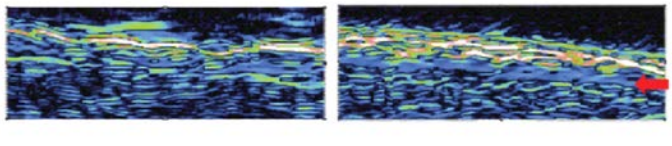


FIGURE 2. Herovici stain – baseline (A) showing magenta-colored mature older collagen fibers transforming into (B) blue-colored fine new fibers indicating neocollagenesis. Observe the new undulating DEJ beginning to form with significantly improved definition of the basement membrane.

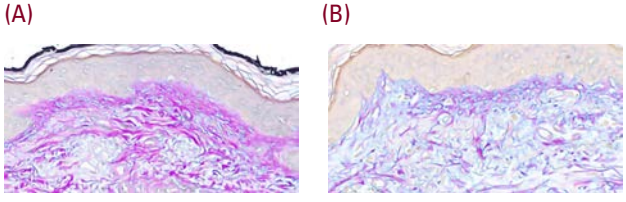
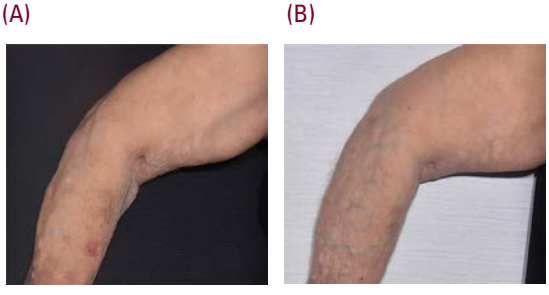


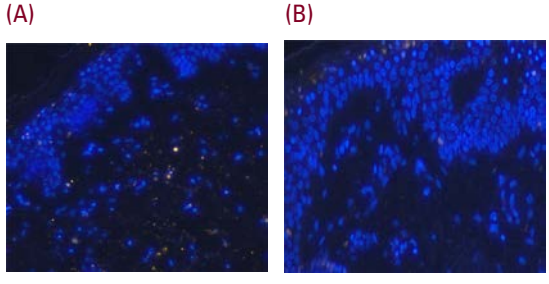
FIGURE 3. Example of R&R treated arm at baseline (B) and after 24 weeks of treatment (A). Note skin tightening, reduction in crepiness, and fewer areas of fragility.



remodeling, with the formation of new healthy collagen and elastin fibers starting in the papillary dermis and progressively extending deeper over time (Figures 2A and B), along with overall stimulation of hyaluronic acid, an important component for treating DP.

Statistically significant improvements were seen in all arm skin parameters at week 24 compared to baseline, as evaluated by the blinded investigators. Overall, the R&R-treated arms exhibited

FIGURE 5. The untreated sample (A) shows signs of senescent cells (yellow spots, p16 stain) in the dermis. The treated sample (B) shows a reduction in senescent cells and signs of renewed cellular proliferation in the dermis.



greater average gains in texture, tone, color, and evenness than the ceramide moisturizer-treated arms at week 24 (Figure 3).

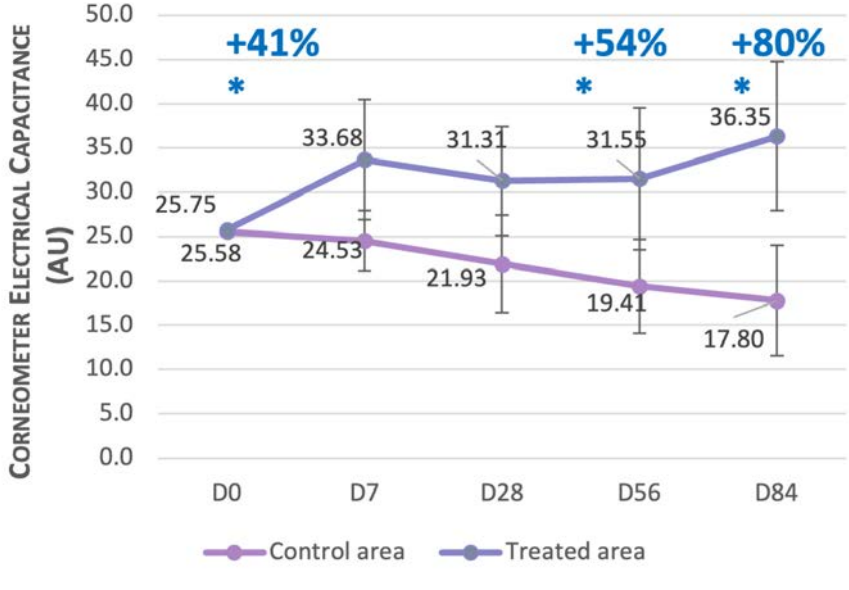
Barrier Integrity, Hydration and Resilience

Applying the micro-mandelic and Centella cream twice daily (Cetaphil firming and hydrating activator cream, Galderma Dallas USA) reducedTEWL by up to 40% and increased hydration by 80% (Figure 4). Ultrasound showed a 5% increase in dermal and epidermal thickness. Patients with sensitive, photodamaged skin demonstrated improved skin resilience, with increases in smoothness, density, and reductions in crepiness and pinch recoil tests—all with excellent tolerability.[6,7]

Impact on Cellular Senescence

Preclinical studies showed that microdosed mandelic acid and Centella asiatica significantly reduced the number of senescent cells (p16 staining), lowered SASP-related cytokines (IL-1β, TNFα, IL-8), and improved cell turnover through JAG/NOTCH pathways. This increase also indicates better barrier function and cellular renewal.[8]

FIGURE 4. Applying Activator cream twice daily significantly improves hydration, as measured by corneometer.



'Anti-aging' Biomarkers

Besides the biological processes discussed earlier in this paper, specific genes and cellular responses have been directly connected to anti-aging concepts. In a separate study testing TriHex technology, it was found to significantly upregulate the Klotho gene and related FGF23, FGFR1, and FOXO3B anti-aging genes. Additionally, the formulation notably reduced telomere shortening compared to the control.[9]

DISCUSSION

These findings highlight a comprehensive approach across the Galderma portfolios focused on skin activation and resilience. Specifically, the targeted areas include structural restoration through ECM remodeling and recycling, along with DEJ reconstitution, which appears to trigger further regenerative changes in the dermis and epidermis. The aging dermal ECM shows an accumulation of fragmented collagen and elastin (solar elastosis), reduced hyaluronic acid, circulating blood sugar that contributes to glycation end products, and diminished autophagy, all leading to poor recycling of major organelles like mitochondria. In essence, cells become fatigued; their mitochondria fail to produce enough energy (ATP, NAD+), reactive oxygen species (ROS) accumulate, inflammaging occurs, and the environment favors the formation of senescent cells.[8-10] The term suggests cells that die quietly and with dignity, but the reality of senescent cells is different. These cells are anything but dormant—their 'zombie'-like nature causes them to release inflammatory cytokines as SASPs, which influence neighboring cells and promote similar changes. Therefore, when senescent cells build up, 'there goes the neighborhood.' Given this cumulative aging process, the strategy of structural repair first—ECM remodeling, autophagy stimulation, mitochondrial replacement to boost energy and reduce ROS, lowering background inflammation, and limiting cellular senescence—is a powerful approach.[8-10] It has shown impressive results with TriHex technology both in pre-conditioning before procedures, immediately afterward, and for long-term maintenance. DP offers an ideal model to test the potential reversal of this degenerative environment to foster regeneration, skin activation, and resilience. The initial study results, demonstrating DEJ reconstitution and ECM remodeling along with waste removal and replacement with healthy, new tissue, represent the ultimate skin waste management and recycling program.[5,10]

On the second front, maintaining barrier integrity, hydration, and skin resilience is crucial as additional support at a superficial level. The Cetaphil activating cream showed excellent rehydrating properties, with significant effects on TEWL, skin thickness, and smoothness.[6-8] Once again, DP provides an ideal environment to test its potential to support and restore reduced tears, bruising, and enhance skin longevity and resilience. Although these results were highly significant, they were not entirely unexpected, given the preclinical data. What was surprising, however, was a significant discovery in our preclinical work: we observed that cells responded strongly to microdoses of active Centella and mandelic acid, leading to a 'hormesis' situation in which small doses ('Goldilocks effect') produced new effects only when combined.[8] These studies showed a decrease in senescent cells and lower SASPs—an important progress in promoting skin health and longevity by removing one of the most damaging factors in skin aging.[8] Having this combination in low, well-tolerated doses for sensitive skin—and producing excellent results, as reported by patients and investigators—marks a significant step forward in cellular reactivation and skin longevity.

Alongside various clinical and pre-clinical studies, we directly addressed the specific hallmarks of aging described earlier in this paper. Therefore, we tested TriHex technology with telomere length investigations, examined the upregulation of specific anti-aging genes in cell lines—particularly the KLOTHO gene—and combined these findings with the clinical improvements observed, again exploring skin longevity through a targeted approach.9

The preclinical, clinical, and condition-modifying results we've observed, especially those related to DP—which we believe is an ideal model for reduced cellular activity and skin longevity—have formed the foundation for developing an integrated strategy targeting biological processes that influence and drive skin activation and longevity. These findings shift and redefine dermatological research from focusing solely on cosmetic improvements to emphasizing measurable resilience, positioning skin activation and longevity as the next frontier.

Future Directions

Building on the concept outlined above, as leaders in the field with numerous preclinical and clinical trials focused on skin activation, we will continue to introduce new innovations and technologies to each product line within the Galderma portfolio. Each will feature unique scientific details and stories, all centered on cellular activation and skin longevity, aligned with the biological processes we've identified that have a significant impact. New ranges and SKUs will embody this philosophy.

CONCLUSION

By integrating structural repair, enhanced barrier integrity, and reduced cellular senescence into a skin activation program, our work redefines 'anti-aging' as 'skin activation' that influences longevity. Preclinical and clinical results, along with imaging, histology, and biomarker studies, have convinced us that skin can not only look younger but also function younger. This establishes a new clinical standard for dermatologic skin longevity through cellular activation or the 'Skin Activation Program'.

DISCLOSURES

Dr. Widgerow is the Chief Scientific Officer of Galderma. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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doi:10.36849/JDD.9148

March 2026 273 Volume 25 • Issue 3

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CASE REPORT

Journal of Drugs in Dermatology

From Bald to Bold: Reversal of Alopecia Totalis in an Adolescent Using Dupilumab Monotherapy

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ABSTRACT

Introduction: Alopecia areata (AA) is an autoimmune condition marked by non-scarring, patchy hair loss of the scalp which progresses in <10% of cases to alopecia totalis (AT), which is marked by complete hair loss from the scalp, eyebrows, and eyelashes. AA is prevalent in pediatric patients and is associated with atopic dermatitis (AD). The interleukin (IL)-4 and IL-13 antagonist dupilumab is approved for use in both pediatric and adult patients with AD and asthma. However, in some cases, dupilumab has shown promising results in regrowing hair in patients with concurrent AA.

Case Presentation: We report a 13-year-old male patient with a past medical history of AD and food atopy, who presented with AA to the scalp. The patient's hormonal lab work-up was within normal limits, and he was treated and failed typical therapies for AA. Within nine months of treatment, the hair loss progressed to AT of the scalp and eyebrows. Dupilumab was then initiated as monotherapy for the patient's AD and AT, leading to regrowth of hair on the scalp and eyebrows within several months and sustained complete hair regeneration after 17 months post dupilumab initiation.

Conclusion: This case demonstrates the potential use of dupilumab, which has a well-established safety profile, for pediatric patients with AA and its ability to initiate and sustain hair growth for the long term. Dermatologists may consider dupilumab for patients with AA and comorbid AD that have failed a variety of treatments from several drug classes.

J Drugs Dermatol. 2026;25(3):273-274. doi:10.36849/JDD.9148

INTRODUCTION

Alopecia areata (AA) is an autoimmune condition which affects roughly 2% of the population globally and is characterized by non-scarring hair loss.[1] AA presents as patchy hair loss on the scalp or beard which, in <10% of AA patients, can expand to alopecia totalis (AT) resulting in complete hair loss on the scalp and often the eyebrows and eyelashes.[2,3] AA pathogenesis involves the loss of immune privilege of the hair follicle because of downregulated proteins that prevent self-antigens from binding with CD8+T Cells during follicular growth.[1] T helper type 1 cells (Th1) and the induction of IFN-γ are major contributors to AA.[1,2]

AA's effect on pediatric patients, especially adolescents, is associated with concurrent atopic dermatitis (AD).[2,3] Dupilumab is an antagonist to interleukin (IL)-4 and IL-13 receptors that is approved for treatment of AD and asthma in pediatric and adult populations. In recent years, dupilumab has shown potential for use in treating AA.[1] This report highlights the use of dupilumab in managing AT in an adolescent male.

CASE REPORT

A 13-year-old male with a history of AD and food atopy presented with two months of progressive scalp hair loss. Examination revealed discrete, non-scarring patches of hair loss on the mid scalp, crown, and parietal regions meeting the criteria for alopecia areata (Figure 1A). The patient was referred to an endocrinologist, and laboratory work-up was within normal limits (Table 1). Initial treatment for the hair loss included topical, oral, and intralesional corticosteroids, among other pharmacologic therapies (Table 1). Despite topical management, nine months after the initial diagnosis, the chronic AA progressed to AT with complete non-scarring hair loss of the scalp and eyebrows (Figure 1B). The patient's concurrent AD had also progressed in severity, failing treatment with oral and topical steroids and calcineurin inhibitors. Dupilumab was initiated for AD, and at the one-month follow-up, signs of patchy hair growth on the scalp were noted. Hair growth continued over the following months with eventual complete hair regrowth on the scalp and eyebrows. This regeneration was sustained on evaluation 17 months post dupilumab initiation (Figure 1C).

TABLE 1.

Patient Demographics and Treatment Details

Demographics	Associated Comorbid Conditions	Laboratory Studies	Failed Treatments	Treatments With Hair Growth Results
Sex: Male Age: 13 years old Race: Asian	Atopic Dermatitis Food Atopy (tree nuts)	CRP, CBC, CMP, ESR, Free T4 and TSH panel, ANA Titer, SARS-CoV-2 Serology, Testosterone Free and Total, TPO Antibody Titer	Fluocinonide 0.05% topical solution Clobetasol 0.05% scalp solution Minoxidil 5% foam Tacrolimus 0.1% topical ointment Ruxolitinib 1.5% topical cream Anthralin1% shampoo Prednisone 50 mg tablet Intralesional Kenalog Injection UVB light therapy	Dupilumab 600 mg Subcutaneous pen injector

CRP, C-reactive protein [Titer] in serum or plasma; CBC, Complete Blood Count W Auto differential panel; CMP, Comprehensive metabolic 2000 panel- serum or plasma; ESR, Erythrocyte sedimentation rate by Westergren method; ANA Titer, Nuclear Ab [Titer] in serum; SARS-CoV-2 Serology, SARS-CoV-2 (COVID-19) IgG+IgM [Presence] in Serum or Plasma by Immunoassay; TPO Antibody Titer, Thyroperoxidase Ab [Titer] in serum or plasma; UVB, ultraviolet B

FIGURE 1. The initial presentation of the patient with AA (A) which progressed to AT (B) and full hair regeneration 17 months post initiation of dupilumab (C)



DISCUSSION

AA has a greater prevalence in pediatric patients, especially females and those of Asian, Black, and Hispanic descent.[2,4] This case expands upon the growing number of reports of hair regeneration in pediatric patients with AA. However, there is little published information at the time of this report on the use of dupilumab to reverse AT in pediatric patients with sustained response in hair regrowth. Conventional treatments for AA include corticosteroids, topical immunotherapy, minoxidil, and JAK/STAT inhibitors. However, treatment outcomes are highly variable, with many experiencing recurrence upon treatment discontinuation.[2] Potential benefits of dupilumab for treatment of AA may be due to pathogenic skewing to Th2 cytokine-mediated follicular destruction in patients with atopic dysfunction. Dupilumab blocks IL-4 and IL-13 receptors, which are both major cytokines produced by Th2, and thus prevents self-antigen binding, allowing the anagen phase of follicular growth to progress.[1,2]

With dupilumab's approval for use in children and its favorable safety profile, there is potential for its use in AA and its subtypes as monotherapy or adjuvant therapy.[5] It is vital for future studies to investigate dupilumab efficacy in short-term reversal of pediatric AA, its capacity for long-term remission, and the extended reduction in the negative impacts on psychological health.[3]

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.9259

March 2026 275 Volume 25 • Issue 3

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CASE REPORT

Journal of Drugs in Dermatology

Treatment Strategy for Refractory Dissecting Cellulitis of the Scalp Using Bimekizumab, Isotretinoin, and Oral Antibiotics

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ABSTRACT

Dissecting cellulitis of the scalp (DCS) is a chronic inflammatory disorder of the scalp that manifests as inflamed nodules and abscesses, with subsequent patchy, scarring hair loss. While its exact pathogenesis remains unclear, follicular occlusion, inflammation, and sinus tract formation are thought to be key contributors. We present two patients, a 26-year-old male and a 33-year-old male, with refractory DCS and concomitant hidradenitis suppurativa and acne conglobata who were successfully treated with a combination therapy regimen of bimekizumab, isotretinoin, and oral antibiotics.

J Drugs Dermatol. 2026;25(3):275-276. doi:10.36849/JDD.9259

INTRODUCTION

Dissecting cellulitis of the scalp (DCS) is a chronic inflammatory disorder of the scalp that manifests as inflamed nodules and abscesses, with subsequent patchy, scarring hair loss.[1] While its exact pathogenesis remains unclear, follicular occlusion, inflammation, and sinus tract formation are thought to be key contributors.[1] DCS is commonly associated with hidradenitis suppurativa (HS), acne conglobata (AC), and pilonidal cysts, collectively known as the follicular occlusion tetrad.[1] The condition can be significantly debilitating due to pain, visual disfigurement, and psychological distress.[1] We present two patients with refractory DCS and concomitant HS and AC who were successfully treated with a combination therapy regimen of bimekizumab, isotretinoin, and oral antibiotics.

CASE REPORTS

A 26-year-old male with a medical history significant for HS and AC presented to our dermatology clinic with a greater than 10-year history of draining sores on his scalp and associated hair loss (Figure 1). At the time of presentation, the patient had already been diagnosed with biopsy-proven DCS from an outside dermatologist. Previously trialed and failed treatments included adalimumab, isotretinoin, oral tetracycline, doxycycline, minocycline, and incision and drainage of the nodules. On physical examination, he had multiple scarring alopecic patches with surrounding erythematous pustules and nodules on the scalp, face, and chest. Although his medical history was also significant for nodules and abscesses within the inguinal folds and chest, they were not observed on exam. The patient was subsequently started on bimekizumab 320 mg, cephalexin 500 mg twice daily, and isotretinoin 40 mg twice daily. At the initial visit, the patient received a loading dose of bimekizumab 320 mg and then switched to bimekizumab 160 mg every two weeks. After 6 weeks following the initial loading dose, the patient achieved complete resolution of scalp lesions (Figure 1). The patient is continuing the bimekizumab 160 mg maintenance dosing, cephalexin 500 mg twice daily, and isotretinoin 40 mg twice daily to maintain clearance of his condition.

FIGURE 1. The 26-year-old patient with erythematous, crusted pustules throughout the scalp before (A) and after treatment (B) with bimekizumab 320 mg every two weeks, isotretinoin 40 mg twice daily, and cephalexin 500 mg twice daily.



A 33-year-old patient from Australia presented with a 4-year history of HS, AC, and DCS, primarily concerned about the increasing number of nodules developing on his scalp and scattered areas of hair loss. He had previously tried and failed

FIGURE 2. The 33-year-old patient with several occipital subcutaneous nodules throughout the scalp before (A) and after treatment (B) with bimekizumab 320 mg every two weeks, isotretinoin 160 mg daily, and cephalexin 500 mg twice daily.



a 6-month course of a "low dose" isotretinoin, a one-year course of adalimumab injections, and 6 months of systemic methotrexate. On physical examination, several mobile, subcutaneous nodules were present on the occipital scalp (Figure 2). Multiple erythematous inflammatory nodules were present on the right cheek and several closed sinus tracts were observed near the groin (Figure 2). The patient was started on 160 mg isotretinoin daily (2 mg/kg), bimekizumab 320 mg every four weeks, and cephalexin 500 mg twice daily. The patient also underwent incision and drainage of his occipital scalp nodule. After returning to Australia, his primary dermatologist continued the isotretinoin dosage and increased the bimekizumab dosage to 320 mg every two weeks. After four months of treatment, the patient reported significant improvement in his AC and reduced frequency of nodule development throughout his scalp (Figure 2).

CONCLUSION

The treatment of DCS is multifactorial and no gold standard treatment exists for this condition.[1] Treatments include tumour necrosis factor-alpha blocking agents, antibiotics, corticosteroids, laser treatment, and surgical excision.[1] Notably, there are a few case reports describing the successful treatment of DCS utilizing interleukin (IL)-23 and IL-17 blockers such as risankizumab and secukinumab, respectively.[2,3] Given that both of our patients previously failed treatment with adalimumab, we opted to utilize biologics targeting different interleukin classes.

IL-17 has been implicated in the pathogenesis of HS and other scarring alopecias like lichen planopilaris.[2,4] While no studies have specifically evaluated the mechanism of IL-17 involvement in the pathogenesis of DCS, there is literature describing the resolution of this condition utilizing secukinumab, another IL-17 blocker.[2] For the treatment of HS, IL-17 blockers like secukinumab and bimekizumab have been extensively studied through various clinical trials.[5] Bimekizumab selectively inhibits IL-17A and IL-17F and is approved for HS.[5] Unlike other IL-17 inhibitors, bimekizumab notably inhibits the IL-17F isomer as well.[5] A preliminary study using a Bayesian anchored indirect comparison of clinical trial data for secukinumab and bimekizumab in HS found that bimekizumab achieved a greater HiSCR 50 response at week 16 compared to secukinumab.[5] A greater response with bimekizumab may be attributed to its IL-17F blocking activity for both HS and DCS.

Given that DCS may concomitantly occur with HS and AC, appropriate treatment selection must account for these comorbid conditions. As demonstrated in our patients who had previously failed various treatment modalities, they achieved significant clearance of their AC, HS, and DCS after treatment with bimekizumab and isotretinoin. Ultimately, in patients with severe DCS refractory to traditional treatments, biologic therapies like bimekizumab should be used.

DISCLOSURES

Authors Lau and Gerstein have no conflicts of interest to disclose. Author Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB, and is a consultant for Aikium, Almirall, AltruBio Inc., Amgen, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education,Forte biosciences, Galderma, Genentech, Incyte, LEO Pharma, Goodrx-Mayne, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Oruka, Pfizer,Sanofi-Regeneron, Revolo, Seanergy, Strata, Sunpharma,Takeda,Trevi, and Verrica.

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doi:10.36849/JDD.9186e

March 2026 277 Volume 25 • Issue 2

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

A Decade of Hair Prosthetic Injuries: A Review of United States Emergency Department Cases (2013-2022)

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INTRODUCTION

Hair prosthetics are widely used to improve the quality of life standards for patients suffering from a variety of hair conditions, such as alopecia.[1] The use of hair prosthetics in the setting of alopecia can critically augment a patient's confidence and social assimilation.[2] Strict care is necessitated while handling hair prosthetics and their fixatives or adhesives; use may cause injury to the hair and scalp.[3] However, current epidemiological data on hair prosthetic injury in emergency settings are limited. This study investigates the epidemiology of hair prosthetic injury-related cases in US emergency departments (EDs) from 2013-2022.

MATERIALS AND METHODS

The National Electronic Injury Surveillance System (NEISS), which collects data from a nationally representative cohort of 100 EDs, was queried on 10/29/2024, using keywords "wig", "wigs", "hairpiece", "hairpieces", "toupe", "toupes", "toupee", and "toupees", and demographic data was collected. T-value tests assessed differences between genders and age (P<0.05).

RESULTS

A total of 88 hair prosthetic-related injury cases were analyzed, with a mean age of 34 years (range: 2–84). Most patients were female (94.1%), 10.2% White race, and 53.4% Black race. From 2013–2022, injuries increased by 56.3% overall (Figure 1). White women more frequently presented with hair prosthetic injuries than White men (10.8% vs 0.0%, P=0.002), and race documentation was less frequent in patients aged 35+ compared to younger patients (46.3% vs 25.5%, P=0.04; Tables 1, 2).

The most common diagnoses included dermatitis, lacerations, and contusions, with no variation by age. Lacerations were more frequently documented in women than men (16.9% vs 0.0%, P<0.001). Patients over 35 and women had more varied diagnoses classified as "other" (36.6% vs 10.6%, P<0.05; 24.1% vs 0.0%, P0.00001). Women more often reported pain from wigs than men (6.0% vs 0.0%, P=0.02).

The most commonly injured body parts included the head, eyes, and ears, with women experiencing significantly more ear

FIGURE 1. Injury Frequency by gender from 2013 to 2022.

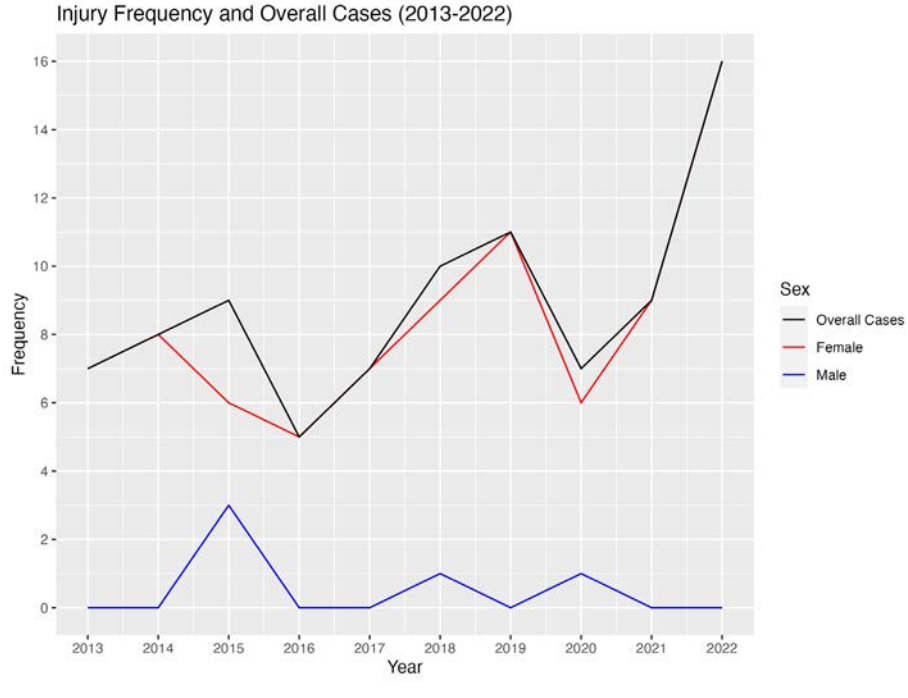


TABLE 1.

Characteristics of Patient Sex, Race, Disposition, Diagnosis, and Injured Body Part by Age

Characteristics	Age <35 Years (n=47), n (%)	Age ≥35 Years (n=41), n (%)	*P*-Value	Total
Sex				
Male	3 (6.38%)	2 (4.88%)	0.762	5
Female	44 (93.62%)	39 (95.12%)	0.762	83
Race				
White	5 (10.64%)	4 (9.76%)	0.893	9
Black/African American	29 (61.70%)	18 (43.90%)	0.098	47
Other	1 (2.13%)	0 (0.00%)	0.323	1
Asian	0 (0.00%)	0 (0.00%)	n/a	0
Native Hawaiian/Pacific Islander	0 (0.00%)	0 (0.00%)	n/a	0
Not Reported	12 (25.53%)	19 (46.34%)	0.044	31
Disposition				
Treated/Examined and Released	44 (93.62%)	35 (85.37%)	0.219	79
Held for Observation	1 (2.13%)	1 (2.44%)	0.924	2
Treated and Admitted/Hospitalized	2 (4.26%)	1 (2.44%)	0.638	3
No Injury	0 (0.00%)	3 (7.32%)	0.083	3
Left without being seen	0 (0.00%)	1 (2.44%)	0.323	1
Diagnosis				
Ingestion	2 (4.26%)	0 (0.00%)	0.160	2
Aspiration	1 (2.13%)	0 (0.00%)	0.323	1
Burn, Chemical	0 (0.00%)	1 (2.44%)	0.323	1
Burns Thermal	1 (2.13%)	2 (4.88%)	0.496	3
Contusions, Abr.	6 (12.77%)	7 (17.07%)	0.578	13
Foreign Body	1 (2.13%)	1 (2.44%)	0.924	2
Fracture	0 (0.00%)	1 (2.44%)	0.323	1
Laceration	10 (21.28%)	4 (9.76%)	0.135	14
Internal Injury	1 (2.13%)	1 (2.44%)	0.924	2
Strain, Sprain	1 (2.13%)	0 (0.00%)	0.323	1
Poisoning	2 (4.26%)	1 (2.44%)	0.638	3
Avulsion	1 (2.13%)	0 (0.00%)	0.323	1
Dermatitis	16 (34.04%)	8 (19.51%)	0.125	24
Other:	5 (10.64%)	15 (36.59%)	0.0047	20
Pain (other)	2 (4.26%)	3 (7.32%)	0.549	5
Headache (other)	0 (0.00%)	3 (7.32%)	0.083	3
Eye Irritation (other)	1 (2.13%)	1 (2.44%)	0.924	2
Otalgia (other)	0 (0.00%)	1 (2.44%)	0.323	1
Hypotension/Syncope (other)	0 (0.00%)	1 (2.44%)	0.323	1
Scalp Abscess (other)	0 (0.00%)	1 (2.44%)	0.323	1
Allergic Reaction (other)	0 (0.00%)	2 (4.88%)	0.160	2
Irritation (other)	0 (0.00%)	1 (2.44%)	0.323	1
Chemical Exposure (other)	1 (2.13%)	0 (0.00%)	0.323	1
Chemical Otitis (other)	0 (0.00%)	1 (2.44%)	0.323	1
Swelling (other)	1 (2.13%)	0 (0.00%)	0.323	1
Wound (other)	0 (0.00%)	1 (2.44%)	0.323	1

TABLE 1. (CONTINUED)

Characteristics of Patient Sex, Race, Disposition, Diagnosis, and Injured Body Part by Age				
Characteristics	**Age <35 Years (n=47), n (%)**	**Age ≥35 Years (n=41), n (%)**	***P*-Value**	**Total**
Body Part				
Internal	3 (6.38%)	0 (0.00%)	0.083	3
Upper Trunk	1 (2.13%)	1 (2.44%)	0.924	2
Wrist	1 (2.13%)	0 (0.00%)	0.323	1
Knee	1 (2.13%)	0 (0.00%)	0.323	1
Lower Leg	1 (2.13%)	0 (0.00%)	0.323	1
Ankle	0 (0.00%)	1 (2.44%)	0.323	1
Head	11 (23.40%)	17 (41.46%)	0.074	28
Face	12 (25.53%)	7 (17.07%)	0.337	19
Eyeball	4 (8.51%)	6 (14.63%)	0.380	10
Lower Trunk	1 (2.13%)	1 (2.44%)	0.924	2
Hand	1 (2.13%)	0 (0.00%)	0.323	1
Foot	1 (2.13%)	0 (0.00%)	0.323	1
All Parts Body	3 (6.38%)	3 (7.32%)	0.865	6
Mouth	1 (2.13%)	0 (0.00%)	0.323	1
Neck	0 (0.00%)	2 (4.88%)	0.160	2
Finger	3 (6.38%)	0 (0.00%)	0.083	3
Ear	3 (6.38%)	3 (7.32%)	0.865	6
Total	47	41	--	88

P-Values were calculated using t-tests at the 95% confidence level.

TABLE 2.

Characteristics of Patient Age, Race, Disposition, Diagnosis, and Injured Body Part by Gender				
Characteristics	**Male (n = 5), n (%)**	**Female (n = 83), n (%)**	***P*-Value**	**Total**
Age				
>=35	2 (40.00%)	39 (0.470)	0.790	41
<35	3 (60.00%)	44 (0.530)	0.790	47
Race				
White	0 (0.00%)	9 (10.80%)	0.002	9
Black/African American	2 (40.00%)	45 (54.20%)	0.599	47
Other	0 (0.00%)	1 (1.20%)	0.320	1
Asian	0 (0.00%)	0 (0.00%)	n/a	0
Native Hawaiian/Pacific Islander	0 (0.00%)	0 (0.00%)	n/a	0
Not Reported	3 (60.00%)	28 (33.70%)	0.349	31
Disposition				
Treated/Examined and Released	4 (80.00%)	75 (90.40%)	0.635	79
Held for Observation	0 (0.00%)	2 (2.40%)	0.159	2
Treated and Admitted/Hospitalized	1 (20.00%)	2 (2.40%)	0.430	3
No Injury	0 (0.00%)	3 (3.60%)	0.083	3
Left without being seen	0 (0.00%)	1 (1.20%)	0.320	1
Treated and Transferred	0 (0.00%)	0 (0.00%)	n/a	0

TABLE 2. (CONTINUED)

Characteristics of Patient Age, Race, Disposition, Diagnosis, and Injured Body Part by Gender				
Characteristics	**Male (n = 5), n (%)**	**Female (n = 83), n (%)**	***P*-Value**	**Total**
Diagnosis				
Ingestion	0 (0.00%)	2 (2.40%)	0.159	2
Aspiration	0 (0.00%)	1 (1.20%)	0.320	1
Burn, Chemical	0 (0.00%)	1 (1.20%)	0.320	1
Burns Thermal	0 (0.00%)	3 (3.60%)	0.083	3
Contusions, Abr.	1 (20.00%)	12 (14.50%)	0.798	13
Foreign Body	0 (0.00%)	2 (2.40%)	0.159	2
Fracture	0 (0.00%)	1 (1.20%)	0.320	1
Laceration	0 (0.00%)	14 (16.90%)	0.000104	14
Internal Injury	1 (20.00%)	1 (1.20%)	0.4009666	2
Strain, Sprain	0 (0.00%)	1 (1.20%)	0.3202524	1
Poisoning	2 (40.00%)	1 (1.20%)	0.1884949	3
Avulsion	0 (0.00%)	20 (24.10%)	0.0000021	20
Dermatitis	0 (0.00%)	1 (1.20%)	0.320	1
Other:	1 (20.00%)	23 (27.70%)	0.725	24
Pain (other)	0 (0.00%)	5 (6.00%)	0.024	5
Headache (other)	0 (0.00%)	3 (3.60%)	0.0830	3
Eye Irritation (other)	0 (0.00%)	2 (2.40%)	0.159	2
Otalgia (other)	0 (0.00%)	1 (1.20%)	0.320	1
Hypotension/Syncope (other)	0 (0.00%)	1 (1.20%)	0.320	1
Scalp Abscess (other)	0 (0.00%)	1 (1.20%)	0.320	1
Allergic Reaction (other)	0 (0.00%)	2 (2.40%)	0.159	2
Irritation (other)	0 (0.00%)	1 (1.20%)	0.320	1
Chemical Exposure (other)	0 (0.00%)	1 (1.20%)	0.320	1
Chemical Otitis (other)	0 (0.00%)	1 (1.20%)	0.320	1
Swelling (other)	0 (0.00%)	1 (1.20%)	0.320	1
Wound (other)	0 (0.00%)	1 (1.20%)	0.320	1
Body Part				
Internal	0 (0.00%)	3 (3.60%)	0.083	3
Upper Trunk	0 (0.00%)	2 (2.40%)	0.159	2
Wrist	0 (0.00%)	1 (1.20%)	0.320	1
Knee	0 (0.00%)	1 (1.20%)	0.320	1
Lower Leg	0 (0.00%)	1 (1.20%)	0.320	1
Ankle	0 (0.00%)	1 (1.20%)	0.320	1
Head	1 (20.00%)	27 (32.50%)	0.573	28
Face	1 (20.00%)	18 (21.70%)	0.938	19
Eyeball	1 (20.00%)	9 (10.80%)	0.674	10
Lower Trunk	0 (0.00%)	2 (2.40%)	0.159	2
Hand	0 (0.00%)	1 (1.20%)	0.320	1
Foot	0 (0.00%)	1 (1.20%)	0.320	1
All Parts Body	2 (40.00%)	4 (4.80%)	0.225	6
Mouth	0 (0.00%)	1 (1.20%)	0.320	1
Neck	0 (0.00%)	2 (2.40%)	0.159	2
Finger	0 (0.00%)	3 (3.60%)	0.083	3
Ear	0 (0.00%)	6 (7.20%)	0.0134	6
Total	5	83	--	88

P-Values were calculated using t-tests at the 95% confidence level.

injuries than men (7.2% vs 0.0%, *P*=0.01). Head and eye injuries did not differ significantly across gender or age.

DISCUSSION

In summary, hair prosthetic injury is on the rise in the US for women and overall cases. Given that Black women comprised 53.4% of injuries, efforts to expand culturally competent education on safe prosthetic handling to this population are warranted. It is also important to consider the cultural implications of hair representation and symbolism for women of color, as discrimination and minimal training can worsen outcomes for this subgroup.[4,5] Area of advocacy includes wig testing, allergy testing, safe removal practices, as well as scalp protectors and cushions.

CONCLUSION

Hair prosthetics are an avenue for patients to address hair changes, improve their self-esteem, and feel empowered over their scalp and hair concerns. However, sub-groups, such as Black women, appear to be disproportionately affected by scalp reactions and prosthetic-related trauma in the ED. Dermatologists are encouraged to increase patient education and preventative measures to minimize prosthetic injury.

DISCLOSURES

The authors have no conflicts of interest.

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doi:10.36849/JDD.9282e

March 2026 282 Volume 25 • Issue 2

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Patient Perspectives and Attitudes Toward the Diagnostic Process for Central Centrifugal Cicatricial Alopecia

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INTRODUCTION

Central Centrifugal Cicatricial Alopecia (CCCA) is a progressive form of scarring alopecia that primarily affects women of African descent.[1] CCCA can be diagnosed clinically through scalp examination and trichoscopy. Scalp examination typically reveals the classic distribution of hair loss, beginning at the vertex of the scalp with progressive, symmetric centrifugal evolution. Trichoscopy may show a peripilar gray or white halo around the base of the hair follicles.[2] However, CCCA may also present with atypical distributions of hair loss, such as patchy, temporal, occipital, and frontal-parietal patterns, which pose a diagnostic challenge.[3-5] In such cases, scalp biopsies are crucial for accurate and timely diagnosis of CCCA, as they minimize further hair loss and associated morbidity. Despite their clinical value, patients may be hesitant to undergo scalp biopsy due to concerns about side effects, scarring, or the potential for additional hair loss.

Patient perspectives on biopsies have been studied in other contexts (eg, breast cancer, colon cancer); however, no research has focused on patient perspectives regarding the scalp biopsy process for hair loss, particularly in those with CCCA. Therefore, a qualitative, cross-sectional study was designed to assess patient perspectives on scalp biopsies to diagnose CCCA. An anonymous survey was distributed to patients with CCCA at University of Pennsylvania-affiliated dermatology clinics, including those who had and had not undergone a scalp biopsy. Patient knowledge, attitudes, and concerns regarding scalp biopsies and factors influencing their decision-making were evaluated.

Among biopsy patients (*n=30*), 90% agreed that a biopsy was necessary to confirm their diagnoses, compared to just 30% of non-biopsy patients (*n=10*) (see Table 1). Similarly, 83% of biopsy patients strongly preferred biopsy over diagnostic uncertainty, highlighting its perceived value in clarifying disease status. Notably, provider education and communication played a critical role. Over 85% of biopsy patients felt their dermatologist adequately explained the procedure and clearly communicated the results. In contrast, 70–90% of non-biopsy patients reported neutral responses regarding biopsy purpose, treatment implications, and overall understanding. This suggests that refusal of biopsy may reflect gaps in patient education rather than true opposition.

Despite these gaps, 68% of all participants indicated willingness to undergo biopsy if their condition worsened, emphasizing a potential openness to the procedure when supported by a clear rationale or need (see Table 1). Importantly, no respondents reported feeling coerced, reinforcing that patient autonomy was preserved during all visits. Additionally, 77% of biopsy patients conducted independent research after diagnosis, indicating an area for improvement in post-diagnostic counseling and education (see Table 2).

Our study highlights the crucial role of effective clinician-patient communication in shaping attitudes toward scalp biopsy for CCCA. Patients who undergo biopsy demonstrate greater understanding, trust, and willingness to accept diagnostic interventions, whereas those who decline often lack the information needed to make informed choices. Enhancing patient education and offering accessible, vetted resources could bridge this divide. By positioning the biopsy as a tool for early intervention, dermatologists can support shared decision-making and improve diagnostic outcomes in this patient population.

TABLE 1.

Patient Perspectives and Attitudes Toward the Role of Scalp Biopsy in Diagnosing Central Centrifugal Cicatricial Alopecia (CCCA). Survey responses are presented from patients who underwent a scalp biopsy (*n=30*) and those who did not undergo a biopsy (*n=10*). Responses are shown as both numerical values and percentages.

Survey Question		Number (N) / frequency (%)		
		Biopsy (*n=30*)	No Biopsy (*n=10*)	Total (*n=40*)
"Do you agree that it was necessary for the doctor to obtain a scalp biopsy to confirm your diagnosis of CCCA?"	Strongly Agree	17 (56.7%)	2 (20.0%)	19 (47.5%)
	Agree	10 (33.3%)	1 (10.0%)	11 (27.5%)
	Neutral	2 (6.7%)	6 (60.0%)	8 (20.0%)
	Disagree	0 (0%)	0 (0%)	0 (0%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
	No Answer	1 (3.3%)	1 (10.0%)	2 (5.0%)
"Scalp biopsies are necessary to diagnose CCCA and other hair loss disorders."	Strongly Agree	16 (53.3%)	1 (10.0%)	17 (42.5%)
	Agree	10 (33.3%)	3 (30.0%)	13 (32.5%)
	Neutral	0 (0%)	6 (60.0)	6 (15.0%)
	Disagree	2 (6.7%)	0 (0%)	2 (5.0%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
	No Answer	2 (6.7%)	0 (0%)	2 (5.0%)
"I would rather get a scalp biopsy instead of being unsure of what type of hair loss I have."	Strongly Agree	19 (63.3%)	2 (20.0%)	21 (53.5%)
	Agree	6 (20.0%)	2 (20.0%)	8 (20.0%)
	Neutral	0 (0%)	3 (30.0%)	3 (7.5%)
	Disagree	3 (10.0%)	2 (20.0%)	5 (12.5%)
	Strongly Disagree	1 (3.3%)	1 (10.0%)	2 (5.0%)
	No Answer	1 (3.3%)	0 (0%)	1 (3.5%)
"There are other ways besides the scalp biopsy to decide if you have CCCA."	Strongly Agree	2 (6.7%)	1 (10.0%)	3 (7.5%)
	Agree	9 (30.0%)	4 (40.0%)	13 (32.5%)
	Neutral	13 (43.3%)	5 (50.0%)	18 (45.0%)
	Disagree	3 (10.0%)	0 (0%)	3 (7.5%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
	No Answer	3 (10.0%)	0 (0%)	3 (7.5%)
"My dermatologist provided enough information about the scalp biopsy for me to make an informed decision on the procedure."	Strongly Agree	9 (30.0%)	2 (20.0%)	11 (27.5%)
	Agree	11 (36.7%)	1 (10.0%)	12 (30.0%)
	Neutral	1 (3.3%)	0 (0%)	1 (3.5%)
	Disagree	1 (3.3%)	3 (30.0%)	4 (10.0%)
	Strongly Disagree	7 (23.3%)	0 (0%)	7 (17.5%)
	No Answer	1 (3.3%)	4 (40.0%)	5 (12.5%)
"My dermatologist did a good job educating me on the procedure of a scalp biopsy"	Strongly Agree	15 (50.0%)	1 (10.0%)	16 (40.0%)
	Agree	11 (36.7%)	1 (10.0%)	12 (30.0%)
	Neutral	1 (3.3%)	7 (70.0%)	8 (20.0%)
	Disagree	1 (3.3%)	0 (0%)	1 (3.5%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
	No Answer	2 (6.7%)	0 (0%)	2 (5.0%)

TABLE 1. (CONTINUED)

Patient Perspectives and Attitudes Toward the Role of Scalp Biopsy in Diagnosing Central Centrifugal Cicatricial Alopecia (CCCA). Survey responses are presented from patients who underwent a scalp biopsy (*n=30*) and those who did not undergo a biopsy (*n=10*). Responses are shown as both numerical values and percentages.

Survey Question		Number (N) / frequency (%)		
		Biopsy (*n=30*)	No Biopsy (*n=10*)	Total (*n=40*)
"My dermatologist did a good job educating me on why I needed a scalp biopsy"	Strongly Agree	14 (46.7%)	0 (0%)	14 (35.0%)
	Agree	12 (40.0%)	2 (20.0%)	14 (35.0%)
	Neutral	3 (10.0%)	7 (70.0%)	10 (25.0%)
	Disagree	0 (0%)	1 (10.0%)	1 (3.5%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
		1 (3.3%)	0 (0%)	1 (3.5%)
"I was educated on how the management or treatment of hair loss would change if I received my scalp biopsy."	Strongly Agree	12 (40.0%)	0 (0%)	12 (30.0%)
	Agree	7 (23.3%)	0 (0%)	7 (17.5%)
	Neutral	8 (26.7%)	9 (90.0%)	17 (42.5%)
	Disagree	1 (3.3%)	1 (10.0%)	2 (5.0%)
	Strongly Disagree	0 (0%)	0 (0%)	0 (0%)
	No Answer	2 (6.7%)	0 (0%)	2 (5.0%)
"If my hair condition continued to worsen after treatment, I would undergo a biopsy [or second biopsy] if recommended by my dermatologist"	Strongly Agree	11 (36.7%)	1 (10.0%)	12 (30.0%)
	Agree	10 (30.0%)	5 (50.0%)	15 (37.5%)
	Neutral	3 (10.0%)	4 (40.0%)	7 (17.5%)
	Disagree	4 (13.3%)	0 (0%)	4 (10.0%)
	Strongly Disagree	1 (3.3%)	0 (0%)	1 (3.5%)
	No Answer	1 (3.3%)	0 (0%)	1 (3.5%)
Did you ever feel pressured or coerced to get a scalp biopsy?	Yes	0 (0%)	0 (0%)	0 (0%)
	No	28 (93.3%)	8 (80.0%)	36 (90.0%)
	No Answer	2 (6.67%)	2 (20.0%)	4 (10.0%)

TABLE 2.

Perceptions of Diagnostic Communication and Engagement with Biopsy-Related Information Among Patients with CCCA. Survey responses are presented from patients who underwent a scalp biopsy (*n=30*), and responses are shown as both numerical values and percentages. "Other" responses (indicated by an asterisk) include self-reported sources such as medical journals, online health libraries, and general search engines (eg, Google, Medline).

Survey Question		Number (N) / frequency (%)
		Biopsy (*n=30*)
Were you offered a copy of your scalp biopsy report?	Yes	21 (70.0%)
	No	7 (23.3%)
	Unsure	2 (6.67%)
	No Answer	0 (0%)
Did you believe that your dermatologist was clear when communicating your scalp biopsy results?	Very Clear	25 (83.3%)
	Somewhat Clear	5 (16.7%)
	Not Clear	0 (0%)
	No Answer	0 (0%)
After receiving your diagnosis did you do any personal research on the results of your scalp biopsy?	Yes	23 (76.7%)
	No	7 (23.3%)
	No Answer	0 (0%)

TABLE 2. (CONTINUED)

Perceptions of Diagnostic Communication and Engagement with Biopsy-Related Information Among Patients with CCCA. Survey responses are presented from patients who underwent a scalp biopsy (*n=30*), and responses are shown as both numerical values and percentages. "Other" responses (indicated by an asterisk) include self-reported sources such as medical journals, online health libraries, and general search engines (eg, Google, Medline).

Survey Question		Number (N) / frequency (%)
		Biopsy (*n=30*)
For respondents that responded yes to the previous question, where did you go to learn more about your results?	Dermatology Websites	17 (56.7%)
	Blogs	5 (16.7%)
	Online Forums	7 (23.3%)
	Social Media	2 (6.67%)
	Family or Friends	2 (6.67%)
	Other Dermatologist	1 (3.33%)
	Other*	8 (26.7%)
	No Answer	0 (0%)

DISCLOSURES

Dr Taylor has served as a consultant, advisory board member, and/or speaker for AbbVie, Arcutis, Armis Scientific, Avita, Beiersdorf, Biorez, Bristol-Myers Squibb, Cara Therapeutics, Dior, Eli Lilly, EPI Health, Evolus, Galderma, GloGetter, Hugel America, Incyte, Johnson & Johnson, L'Oreal USA, MedScape, MJH LifeSciences, Pfizer, Piction Health, Sanofi, Scientis US, UCB, and Vichy Laboratoires. She has received royalties from McGraw-Hill. She has served as an investigator for Allergan, Concert Pharmaceuticals/Sun Pharma, Croma-Pharma GmbH, Eli Lilly, and Pfizer. Dr. Ogunleye has served as a consultant, advisory board member, and/or speaker for Beiersdorf, MJH LifeSciences, Dermatology Times, Veradermics, and Health Central. All other authors have no conflicts of interest to disclose.

IRB approval status: Reviewed and approved by the University of Pennsylvania IRB (# IRB number: 853013)

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doi:10.36849/JDD.9362e

March 2026 286 Volume 25 • Issue 2

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Baricitinib-Related Adverse Events in Alopecia Areata and Rheumatoid Arthritis: A Comparative Study

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INTRODUCTION

In 2021, the United States Food and Drug Administration (FDA) updated the boxed warnings for three JAK inhibitors (JAKi) following results from a post-marketing safety study of tofacitinib rheumatoid arthritis (RA) patients, which revealed increased risks of adverse events of special interest (AESIs) such as major adverse cardiovascular events (MACE) and malignancies.[1,2] Baricitinib, one of the JAKis subject to the revised warning, was approved in 2022 for the treatment of alopecia areata (AA), a condition that typically affects a younger and healthier population. Given that the revised warnings were based on data from an RA cohort, there is a need for a comparative study discerning risks for AESIs between the two groups.[3]

MATERIALS AND METHODS

This retrospective cohort study utilized TriNetX, a global health research network of de-identified electronic health record data, to identify patients with a diagnosis of AA (ICD-10 L63) or RA (ICD-10 M05.9, M06) who were prescribed baricitinib between March 2006 and March 2025. Demographic and clinical characteristics were first evaluated in unmatched cohorts, then age-sex-race matching was performed to assess differences in AESI outcomes.

RESULTS

The RA cohort was older (mean age 60 vs 37.9 years), had a higher proportion of females (75.7% vs 65.4%), and exhibited a greater prevalence of comorbidities, including hypertension,

TABLE 1.

Clinical Characteristics of Alopecia Areata (AA) and Rheumatoid Arthritis (RA) Patients on Baricitinib

Characteristics	RA n=3073	AA n=1565	*P*-value*
Age, mean (SD)	60.15 +/- 14.2	37.79 +/- 16.7	<0.0001
Sex, no (%)			
Female	2327 (75.7)	1024 (65.4)	<0.0001
Male	709 (23.1)	527 (33.7)	<0.0001
Unknown	37 (1.2)	14 (0.9)	0.360
Race, no (%)			
White	1759 (57.2)	893 (57.1)	0.907
Black or African American	238 (7.8)	213 (13.6)	<0.0001
Asian	201 (6.5)	129 (8.2)	0.037
Other/unknown race	90 (2.9)	100 (6.4)	<0.0001
Comorbidities, no (%)			
Essential hypertension	1344 (43.7)	197 (12.6)	<0.0001
Overweight and obesity	773 (25.2)	178 (11.4)	<0.0001
Type 2 diabetes mellitus	625 (20.3)	64 (4.1)	<0.0001
Tobacco use	128 (4.2)	20 (1.3)	<0.0001
Nicotine dependence	422 (13.7)	77 (4.9)	<0.0001
Concomitant immunomodulating medications, no (%)			
Prednisone	1432 (46.6)	479 (30.6)	<0.0001
Methotrexate	1153 (37.5)	194 (12.4)	<0.0001
Hydroxychloroquine	921 (30)	95 (6.1)	<0.0001
Other (Cyclosporine, Azathioprine, Mycophenolate Mofetil)	389 (12.7)	134 (8.6)	<0.0001
Rituximab	256 (8.3)	10[A] (0.64)[A]	<0.0001

AA, Alopecia areata; RA, Rheumatoid arthritis; SD, Standard Deviation [A]The value is between 1 and 10, listed as 10 for patient privacy.
*: *P*-values were adjusted for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) correction.

TABLE 2.

Adverse Events of Special Interest (AESI) Following Baricitinib Initiation in Patients with Alopecia Areata (AA) and Rheumatoid Arthritis (RA) Cohorts Matched by Age, Sex, and Race With *P*-values

Adverse event of special interest (AESI)[D]	RA, no (%)	AA, no (%)	Odds Ratio (RA/AA)	*P*-value*
Infections				
Infections (general)	136 (28.6)	60 (10.9)	3.29	<0.0001
Urinary tract infection	64 (8.3)	10 (1.2)[C]	7.41	<0.0001
Rare opportunistic infection[A]	59 (7.8)	17 (2.1)	3.94	<0.0001
Upper respiratory tract infection	58 (7.5)	17 (2.2)	3.67	<0.0001
Cardiovascular				
Hypertension	89 (15.1)	19 (2.6)	6.74	<0.0001
Other cardiovascular disorders[B]	87 (12.8)	16 (2.0)	7.07	<0.0001
Acute myocardial infarction	13 (1.5)	10 (1.1)[C]	1.34	0.541
Cerebral infarction	18 (2.0)	10 (1.1)[C]	1.85	0.142
Thromboembolic events	23 (2.7)	10 (1.1)[C]	2.43	0.027
Malignancies				
Non-lymphoma/non-hematologic	86 (12.4)	50 (8.7)	1.5	0.043
Lymphomas/hematologic	10 (1.1)[C]	10 (1.1)[C]	1.01	0.986

RA, Rheumatoid arthritis
[A]Candidiasis, CMV, HSV, Pneumocystosis, TB, Zoster, Histoplasmosis, Cryptococcosis. [B]Includes rheumatic heart diseases, non-myocardial infarction ischemic heart diseases, pulmonary heart disease, diseases of arteries/arterioles/capillaries, other and unspecified disorders of the circulatory system. [C]The value is between 1 and 10, listed as 10 for patient privacy. [D]Patients that were diagnosed with these outcomes prior to the initiation of baricitinib were excluded from the analysis. *: *P*-values were adjusted for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) correction.

obesity, and type 2 diabetes mellitus, compared to the AA cohort. They were also more likely to have received concomitant immunosuppressive therapies prior to baricitinib initiation (Table 1). The AA cohort included higher proportions of Black (13.6% vs 7.8%) and Asian patients (8.2% vs 6.5%).

Matched outcome analysis showed no statistically significant differences in rates of cerebral infarction, acute myocardial infarction, or lymphomas/hematologic malignancies. However, RA patients showed significantly higher odds of urinary tract infections (OR=7.41), other cardiovascular disorders (OR=7.07), hypertension (OR=6.74), rare opportunistic infections (OR=3.94), upper respiratory tract infections (OR=3.67), general infections (OR=3.29), thromboembolic events (OR=2.43), and non-lymphoma/non-hematologic malignancies (OR=1.5) (Table 2).

DISCUSSION

These findings indicate that while baricitinib is associated with higher AESI risk in RA patients, AA patients may have a more favorable safety profile due to fewer baseline comorbidities and less concomitant immunosuppression.[4,5] Nevertheless, the boxed warning remains relevant for both populations, as certain AESIs, including infections, thromboembolic events, and malignancies, though less frequent in AA, were still observed. Given the expanding use of JAKis in dermatology, ongoing pharmacovigilance and tailored risk-benefit assessments are essential, particularly in younger AA patients where long-term safety data are limited. Study limitations include a short follow-up duration, a relatively small sample size limiting multivariate adjustments, and potential dosing variability (2 mg for RA, 2–4 mg for AA). Larger, longer-term studies are needed to validate these findings and improve patient management.

DISCLOSURES

The authors have no conflict of interest to declare.

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doi:10.36849/JDD.9236e

March 2026 288 Volume 25 • Issue 3

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Regrowth of Eyebrows in a Previous Steroid Non-Responder With Alopecia Universalis After Ritlecitinib Treatment

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Dear Editor,

This report highlights that intralesional corticosteroids may serve as adjunctive therapy in alopecia areata patients who were initially steroid non-responders after a period of treatment with Janus kinase inhibitors such as ritlecitinib. While the patient described in this case did not experience eyebrow regrowth while receiving ritlecitinib alone, adjunctive intralesional triamcinolone led to sustained eyebrow hair regrowth in this previous steroid non-responder.

A male patient in his early twenties with treatment-resistant alopecia universalis since age 2 years initially presented to the dermatology clinic in 2019. The patient was enrolled in a clinical trial in which he received ritlecitinib since 2019. At the time of enrollment, his Severity of Alopecia Tool (SALT) score was 100%. Prior to this, the patient had been a non-responder to intralesional corticosteroid injections, clobetasol cream, topical 5% minoxidil, and hydrocortisone 2.5% cream, with minimal response to bimatoprost 0.03% solution to the eyelashes. After initiating ritlecitinib, the patient experienced full scalp hair regrowth at the 24-week primary endpoint of the clinical trial. In early 2024, the patient's SALT score is 0%.

Despite full regrowth of scalp hair while on ritlecitinib 50mg daily, the patient's eyelashes and eyebrows remained without hair (Figure 1). In early 2024, 3 mg/cc triamcinolone acetonide injections were initiated in the eyebrows, as intralesional corticosteroids are the preferred treatment for eyebrow loss in alopecia areata patients. Despite the patient's previous history as a non-responder to intralesional corticosteroid injections, impressive and sustained regrowth of the patient's eyebrows was noted following a series of eleven intralesional triamcinolone treatments (Figure 2). This report highlights the first documented case of a patient who, initially refractory to intralesional corticosteroid injections, became responsive after beginning oral ritlecitinib.

Alopecia areata/universalis represents non-scarring forms of hair loss driven by the dysregulation of various T cell-mediated pathways. The formation of autoantigens in the hair follicle leads to overactivation of proinflammatory cytokines, which subsequently bind the hair follicle. This binding activates immune-mediated pathways and leads to the production of perforins and granzymes via the JAK-STAT pathway. Eventually, patients experience perforin and granzyme-induced apoptosis of the hair follicle.[1] Alopecia areata/universalis is thought to have a genetic predisposition. This patient did not have a family history of hair loss of any type, however. There is no known long-term, absolute cure for alopecia areata, but corticosteroids, squaric acid, minoxidil, calcipotriol, and tacrolimus have been utilized to treat this autoimmune condition.[1,2] An emerging realm of treatment for alopecia areata includes Janus kinase

FIGURE 1. Lack of eyebrow regrowth in this patient with alopecia areata, despite full regrowth of scalp hair after receiving ritlecitinib (this clinical photograph is from prior to the initiation of intralesional triamcinolone).



FIGURE 2. Eyebrow hair regrowth demonstrated in this alopecia areata patient taking ritlecitinib following a series of eleven 3mg/mL intralesional triamcinolone injections at one-month intervals.



(JAK) inhibitors. In a Phase 2b/3 randomized, double-blind, placebo-controlled clinical trial, ritlecitinib, a JAK3/TEC family kinase inhibitor, significantly reduced hair loss in adults with at least 50% SALT scores with alopecia areata by the primary endpoint at week 24.[3] 25-50% of the adolescents randomized in the ritlecitinib Phase 2b/3 trial had a SALT score ≤20 by week 48.[4] In 2023, ritlecitinib 50 mg was approved by the Food and Drug Administration in the United States for the treatment of severe alopecia areata in patients 12 years of age and above.

In addition to its effectiveness in treating alopecia universalis in this patient, ritlecitinib may have also influenced the patient's underlying response to intralesional corticosteroids. There is a possibility that ritlecitinib modulated the immunologic pathways involved in the patient's steroid response, facilitating the regrowth of the patient's eyebrow hair, which had previously been recalcitrant to therapy. Improvements in the alopecia areata lesional phenotype due to JAK inhibition were reported in a biopsy sub-study during the ritlecitinib trials.[5] The potential interactions between ritlecitinib and various immunologic pathways warrant further investigation, as these may have broader implications in the treatment of refractory alopecia areata/universalis.

DISCLOSURES

Dr Hebert has the following COI: Research grants paid to the medical school: Pfizer; Honoraria for speaking and advisory work: Pfizer. Dr Jafari has the following COI: researcher for Pfizer. Dr. Thomas has the following COI: Honoraria for consulting: Regeneron. Ms. McGee has no conflicts of interest to disclose.

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doi:10.36849/JDD.9324R1

March 2026 290 Volume 25 • Issue 3

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Emerging Therapeutic Strategies in Central Centrifugal Cicatricial Alopecia: A Review of the Clinical Trial Landscape

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INTRODUCTION

Central Centrifugal Cicatricial Alopecia (CCCA) is an irreversible primary scarring alopecia impacting up to 5.6% of Black women with significant diagnostic and therapeutic challenges.[1] This study aims to review the current clinical trial landscape for CCCA therapeutics.

The terms "Central Centrifugal Cicatricial Alopecia", "CCCA", and "scarring alopecia" were searched on ClinicalTrials.gov. Data was extracted for all clinical trials investigating CCCA interventions from 2005 to January 2025. Thirteen clinical trials were found and analyzed, encompassing 12 therapies for CCCA (Table 1). Six studies were marked as "complete" with published results on ClinicalTrials.gov or PubMed. Seven studies marked as "active" or "recruiting" had no results yet available.

Brepocitinib, a tyrosine kinase 2/JAK1 inhibitor significantly reduced clinical severity scores (*NCT05076006*).[3] Ritlecitnib, a JAK3 and tyrosine protein kinase inhibitor, resulted in greater improvement of scalp tissue at 24 weeks when compared to brepocitinib (*NCT05549934*).[3] In clinical trial *NCT03346668*, topical gabapentin improved physician-documented hair growth.[5]

Some trials didn't show improvement with the investigated treatment. In *NCT03521687*, while apremilast resulted in slight quality of life improvement, there wasn't significant hair loss improvement.[4] Similarly, microneedling (*NCT04342091*) and platelet-rich plasma (*NCT04472715*) didn't significantly improve alopecia severity scores or hair graft survival, respectively.[2,4]

The increasing number of CCCA clinical trials over the past two decades underscores a growing commitment to advancing targeted therapies and improving outcomes for patients with CCCA (Figure 1).

TABLE 1.

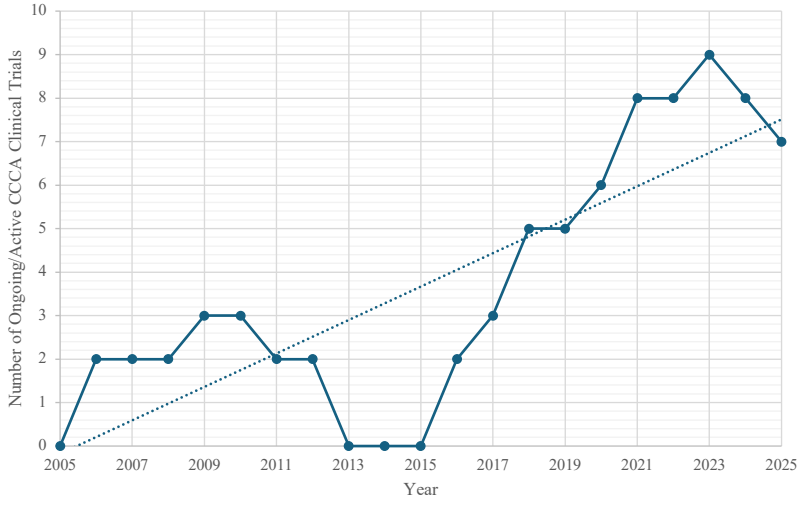
Summary of 13 Clinical Trials on CCCA Interventions from 2005- January 2025 as Described on Clinicaltrials.Gov.

NCT05076006	Brepocitinib monotherapy 45 mg QD vs placebo; 24 weeks	Complete	Brepocitinib downregulated CCL5 expression and significantly reduced clinical severity scores after 24 weeks, with continued improvement through week 48. Fibrotic marker expression worsened in placebo group.[3]
NCT05549934	JAK3/TEC inhibitor Ritlecitinib: 200 mg QD 8 weeks, then 100 mg QD 40 weeks	Active, preliminary results posted	At week 12, greater scalp tissue improvement with brepocitinib. By week 24, improvements were greater with ritlecitinib.[4] At week 24, both ritlecitinib and brepocitinib demonstrated improvement exceeding 100% in the lesional scalp transcriptome toward a non-lesional profile.
NCT03521687	Apremilast 30 mg BID	Complete, 15 patients	Mean change in Physician Global Assessment of Improvement at 24 weeks: 0.07. DLQI total score at Week 24 as compared to Baseline: -2.18. Mean change in Visual Analog Scale at Week 24: -1.94; Mean change in Central Hair Loss Grade at 24 weeks: -0.44.[4]
NCT03346668	Topical gabapentin 6% solution, 1mL BID; 12 weeks	Complete, 1 patient	Improvement of lymphocytic primary cicatricial alopecia symptoms, Lichen Planopilaris Activity Index scores, and physician documented hair growth by third visit. Significant reduction in symptoms; no effect on nerve fiber density or neuropeptide expression.[4]
NCT04472715	Follicular unit transplant vs. follicular unit extraction with PRP before/after transplant	Complete, 20 patients	Follicular unit extraction is preferred procedure with few side effects. PRP didn't significantly affect survival rate of hair grafts.[4]

TABLE 1. (CONTINUED)

Summary of 13 Clinical Trials on CCCA Interventions from 2005- January 2025 as Described on Clinicaltrials.Gov.			
NCT04342091	SOL Nova Device tattoo machine: One monthly microneedling session; 6 months	Complete, 5 patients	Change in skin appearance in treated area noted by investigators and participants with increased pinpoint bleeding. Microneedling didn't improve SALT score over six months in fibrosing alopecia subgroups.[4]
NCT05759338	Revian Red All LED cap QD; 6 months	Complete, no results posted	n/a
NCT04764331	Revian Red All LED cap QD for 6 months; 620 nm vs 660 nm	Recruiting	n/a
NCT05416333	Azelaic acid QD; 6 months	Recruiting	n/a
NCT04207931	Topical steroid + oral doxycyline + topical minoxidil vs Topical steroid + intralesional kenalog + topical minoxidil; 8 months	Recruiting	n/a
NCT03491267	Fractionated CO2 laser with/ without retinoic acid	Recruiting	n/a
NCT05460611	Sciton HALO 1470nm Non-ablative laser	Recruiting	n/a
NCT03078686	Emulsified adipose-derived tissue stromal vascular fraction + PRP vs. adipose-derived cellular stromal vascular fraction	Recruiting	n/a
NCT03078686	Emulsified adipose-derived tissue stromal vascular fraction + PRP vs. adipose-derived cellular stromal vascular fraction	Recruiting	n/a

FIGURE 1. Total number of ongoing/active registered clinical trials for CCCA per year.



DISCLOSURES

Dr Callender has served as an investigator, consultant, or speaker for Almirall, Aerolase, AbbVie/Allergan Aesthetics, Arcutis, Avava, Beiersdorf, Eirion Therapeutics, Eli Lilly, Galderma, Incyte, Janssen, Jeune Aesthetics, L'Oréal, Ortho Dermatologics, Pfizer, Prollineum, Regeneron, SkinBetter Science, SkinCeuticals, Symatese, Teoxane, UpToDate and Veradermics. Miss Garg has no conflicts of interest or disclosures.

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doi:10.36849/JDD.9732

March 2026 292 Volume 25 • Issue 3

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Impact of TNF-α and IL-17 Biologics on Cardiometabolic Outcomes in Hidradenitis Suppurativa: Retrospective Cohort Study

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by painful nodules, abscesses, and sinus tracts. Beyond cutaneous symptoms, HS is associated with increased risk of metabolic and cardiovascular comorbidities such as obesity, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus (T2DM).[1] Guideline-approved biologics for moderate-to-severe HS include the TNF-α inhibitor adalimumab and IL-17 inhibitors secukinumab and bimekizumab.[2] While effective for skin disease, their impact on T2DM and other cardiometabolic comorbidities in HS patients remains largely unexplored in large cohort studies.

Using the TriNetX Research Network (>130 million patients across 80 US healthcare organizations), adults ≥18 years with HS were identified by ≥2 ICD-10 diagnoses (L73.2) at least one month apart. Patients treated with adalimumab, secukinumab, or bimekizumab were categorized as the biologic cohort and matched 1:1 for age, sex, and race to patients not treated with biologics. The primary outcome was incident T2DM after HS diagnosis. Secondary outcomes included cardiovascular events of myocardial infarction, stroke, and heart failure, in addition to healthcare utilization (emergency department [ED] visits and hospitalizations). A secondary analysis compared these same outcomes between TNF-α and IL-17 inhibitor users. Patients with outcomes prior to HS diagnosis were excluded from the analyses.

Out of 291,283 patients with HS, 11,669 patients were treated with biologics and 104,076 were not. In the biologic group compared to no biologic use, the mean age was 37.1 vs 36.9 years, respectively, both with over 70% female predominance. 11,669 patients were matched in each cohort. Patients receiving biologic therapy had a significantly (P<0.05) lower risk of developingT2DM, myocardial infarction, stroke, and heart failure compared to matched HS patients not treated with biologics. ED visits and hospitalizations were also reduced. When comparing biologic classes, 10,294 patients were treated with adalimumab (TNF-α inhibitor) and 3,336 with secukinumab or bimekizumab (IL-17 inhibitors). In the TNF-α group compared with IL-17 inhibitors, the mean age was 36.7 vs 39.0 years, respectively, both with over 70% female predominance. 3,336 patients were matched in each cohort. HS patients treated with IL-17 inhibitors had a significantly (P<0.05) lower risk of developing T2DM, myocardial infarction, and heart failure, compared to patients on TNF-α inhibitors. ED visits and hospitalizations were also reduced in the IL-17 inhibitor cohort (Table 1).

TABLE 1.

Comparison of Outcomes Between Hidradenitis Suppurativa Patients on Biologics vs Without Biologics and TNF-α vs IL-17 Inhibitors After Matching

Outcome	Risk Difference: Biologics to without Biologics	*P*-value	Risk Ratio (95% CI)	Risk Difference: TNF-α to IL-17 Inhibitors	*P*-value	Risk Ratio (95% CI)
T2DM	–0.87%	0.03	0.90 (0.82, 0.99)	+4.42%	< 0.0001	2.09 (1.66, 2.62)
Myocardial Infarction	–0.56%	0.0003	0.67 (0.53, 0.83)	+0.58%	0.02	1.89 (1.12, 3.20)
Stroke	–0.35%	0.01	0.73 (0.58, 0.94)	+0.24%	0.28	1.35 (0.78, 2.34)
Heart Failure	–0.77%	0.0007	0.77 (0.66, 0.90)	+2.47%	< 0.0001	3.27 (2.24, 4.78)
Emergency Department Visits	–4.89%	< 0.0001	0.79 (0.74, 0.85)	+10.14%	< 0.0001	2.21 (1.84, 2.67)
Hospitalizations	–3.20%	< 0.0001	0.83 (0.77, 0.89)	+8.36%	< 0.0001	2.07 (1.74, 2.48)

Biologic therapy in HS was associated with reduced cardiometabolic risk and lower healthcare utilization. These findings suggest potential systemic benefits of biologics beyond skin disease control. Current literature in psoriasis suggests cardioprotective effects of TNF-α and IL-17 inhibition, which may extend to HS, but further research to understand these mechanisms are needed.[3]

This study is limited by reliance on ICD-10 coding, including potential diagnostic misclassification and unknown medication adherence. Future research should investigate the mechanisms by which TNF-α and IL-17 affect systemic metabolic and cardiovascular pathways in HS.

These results underscore the importance of considering cardiometabolic comorbidities when selecting biologic therapies for HS, as treatment choice may affect not only skin disease but also systemic health.

DISCLOSURES

Dr Taylor has served as a consultant, advisory board member, and/or speaker for AbbVie, Arcutis, Armis Scientific, Avita, Beiersdorf, Biorez, Bristol-Myers Squibb, Cara Therapeutics, Dior, Eli Lilly, EPI Health, Evolus, Galderma, GloGetter, Hugel America, Incyte, Johnson & Johnson, L'Oreal USA, MedScape, MJH LifeSciences, Pfizer, Piction Health, Sanofi, Scientis US, UCB, and Vichy Laboratories. Authors Li, Baker, and Alomary have no conflicts to disclose.

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doi:10.36849/JDD.#9767

March 2026 294 Volume 25 • Issue 3

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Journal of Drugs in Dermatology

Exploring the Potential Link Between Minoxidil Use and Rosacea Using A Real-World Data Base

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INTRODUCTION

Minoxidil is a vasodilator used at higher doses as an anti-hypertensive, while low doses of oral minoxidil (LDOM) (between 0.25 and 5 mg) are effective in treating alopecia disorders. Rosacea is characterized by various subtypes, including erythematotelangiectatic, papulopustular, phymatous, and ocular.[1]

We have encountered patients with erythematotelangiectatic rosacea (ETR) who report flushing and worsening of their facial redness with use of LDOM (authors' unpublished data). To explore the association between ETR and use of LDOM, we analyzed real-world data, hypothesizing that use of vasodilatory medications like LDOM may disrupt cutaneous vascular homeostasis of ETR.

MATERIALS AND METHODS

Using TriNetX, we performed a retrospective study using anonymous electronic medical records. Patients diagnosed with "non scarring hair loss" (ICD-10 code L65) between 2005 and 2025 were 1:1 propensity score matched to patients with hair loss not treated with minoxidil (ICD-10 codes Z00.00 and Z00.129), based on age and race/ethnicity, using nearest-neighbor matching with a 0.1 caliper. Covariate balance post-matching was assessed via standardized mean differences (SMD), with SMD <0.1 indicating acceptable balance. This analysis compared the outcomes of two cohorts: Cohort A (58,099 patients, hair loss plus minoxidil) and Cohort B (892,040 patients, hair loss minus minoxidil).

Logistic regression framework calculated odds ratios (OR), risk ratios (RR), and risk differences (RD) to assess the association between minoxidil use and rosacea, a disease of capillaries, rhinophyma, other rosacea, rosacea conjunctivitis, and flushing. Wald 95% confidence intervals were computed, and statistical significance was defined as $P<0.05$ using two-sided z-tests.

RESULTS

Compared with matched controls, individuals using minoxidil (topical and oral) for "other non-scarring hair loss" had significantly higher odds of rosacea (OR 1.282; 95% CI, 1.156-1.423), other rosacea (OR 1.183; 95% CI, 1.010-1.385), rosacea conjunctivitis (OR 7.585; 95% CI, 3.550-6.206), and flushing (OR 0.869; 95% CI, 0.763-0.989) (Table 1). After adjusting for covariates, diseases of capillaries ($P=0.628$), perioral dermatitis ($P=0.232$), and rhinophyma ($P=0.139$) were not statistically significant (Table 1). All other comorbidities were statistically significant in univariate and multivariate analysis ($P<0.05$; Table 1).

DISCUSSION

Physiologically, minoxidil causes arteriolar vasodilation[2]; though the exact mechanism of hair regrowth is unknown, it is speculated that the vasodilatory properties contribute to increased oxygen, blood, and nutrient delivery to the hair follicle.[3] Rosacea is a condition primarily affecting the face, causing flushing and redness. Dysregulation of cutaneous blood flow and upregulation of vasodilatory molecules may contribute to the disease.[1] Minoxidil use and rosacea exacerbation may be

TABLE 1.

Odds Ratio and Risk Difference Percentage for Rosacea-Related Outcomes in Patients Taking Oral or Topical Minoxidil

	Univariate Odds Ratio	[CI]	% Risk Difference	[CI]%	*P*-value
Rosacea	1.282	[1.156, 1.423]	0.2	[0.1, 0.2]	<.001
Diseases of capillaries	1.034	[0.903, 1.185]	0	[-0.0, 0.1]	0.628
Rhinophyma	0.848	[0.682, 1.055]	0	[-0.1, 0.0]	0.139
Other rosacea	1.183	[1.010, 1.385]	0	[-0.0, 0.1]	0.037
Rosacea Conjunctivitis	7.585	[3.550, 16.206]	0	[0.0, 0.0]	<.001
Flushing	0.869	[0.763, 0.989]	-0.1	[-0.1, -0.0]	0.033

CI, confidence interval

explained by its vasodilatory effects, as more blood is delivered to peripheral vascular regions, which are characterized by larger and nearer to the surface vessels.[1] Thus, clinical caution should be taken when prescribing minoxidil to patients with vascular conditions like ETR.

Due to the cross-sectional design, our analysis is limited in temporal causation and reliance on electronic health records, which can introduce misclassification and selection bias. Additionally, we could not distinguish between oral/topical minoxidil use, which differ in their systemic side-effect profile. Prospective studies are warranted to explore the pathophysiological mechanisms that drive these associations, including dose-dependent risk analysis and possible disease exacerbations.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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March 2026 297 Volume 25 • Issue 3
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FEATURED CONTENT
Journal of Drugs in Dermatology

NEWS, VIEWS, AND REVIEWS

A Brighter Outlook for Photodermatoses: Emerging Adjuvant and Photoprotective Therapies

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INTRODUCTION

Photodermatoses are disorders characterized by abnormal cutaneous reactions to ultraviolet radiation (UVR) or visible light.[1] They are categorized as idiopathic, endogenous, or due to exogenous agents.[1] Idiopathic photodermatoses include polymorphic light eruption, juvenile spring eruption, hydroa vacciniforme-like lymphoproliferative disorder, actinic prurigo, chronic actinic dermatitis, and solar urticaria.[1,2] Among the idiopathic photodermatoses, polymorphic light eruption is the most common, with an estimated prevalence of 10% among the general population.[3] The pathophysiology is thought to result from UVR triggering immune dysregulation, resulting in autoimmunity and development of erythematous papules, vesicles, or plaques within hours of sun exposure with associated itch and/or burning.[2,4] Endogenous photodermatoses are inherently phototoxic disorders. They primarily comprise the porphyrias, which are genetic disorders in heme metabolism that lead to porphyrin accumulation. Upon UVR exposure, affected individuals may develop photosensitivity, crusted lesions, bullae, and scarring.[1,5]

Exogenous photodermatoses are classified as phototoxic or photoallergic reactions.[1] Phototoxic reactions occur when a drug or chemical absorbs UVR and directly damages skin cells, leading to exaggerated sunburn-like erythema, edema, or blistering.[1,6] Common causative agents include sparfloxacin, doxycycline, ciprofloxacin, voriconazole, hydrochlorothiazide, naproxen, and other non-steroidal anti-inflammatory drugs.[6] In contrast, photoallergic reactions are immune-mediated, delayed hypersensitivity responses that develop only in previously sensitized individuals.[1] A recent analysis of photopatch testing in 363 patients with suspected photoallergic contact dermatitis (PACD) identified a 20% PACD prevalence, with sunscreens containing benzophenones, antimicrobials, and fragrances as the most common allergens.[1] Key features of photodermatoses are summarized in Table 1.

Photodermatoses have substantial impacts on quality of life and daily practices such as clothing choices, employment, and social life, underscoring the need for adequate treatment.[7]

In the absence of standardized management guidelines, this review summarizes current photodermatoses therapies and highlights emerging preventive and treatment strategies.

Photodermatoses Management

Prevention

While sunscreens primarily protect against UVR by absorbing or reflecting radiation, formulations that combine physical filters, such as titanium dioxide and iron oxide, with DNA repair enzymes, including photolyase and endonuclease, enhance photoprotection in patients with photodermatoses.[1,8] Physical filters provide broad-spectrum UVR and visible light protection, while DNA repair enzymes help reverse UV-induced DNA damage.[1,8]

Oral and topical photoprotective adjuvants have gained attention for their ability to prevent UV damage and may benefit patients with photodermatoses. Polypodium leucotomos extract (PLE) is derived from the Polypodium leucotomos fern and has an extensive

Table 1. Key Features of Polymorphous Light Eruption, Solar Urticaria, Photoallergic Dermatitis, and Cutaneous Porphyria

Diagnosis	Onset	Duration of Lesions	Morphology	Distribution	Associated Features	Pathophysiology
Polymorphous Light Eruption	Hours to days after UV exposure[2,4]	Several days[4]	Monomorphic erythematous papules, vesicles, or plaques[4]	Neck, head, upper extremities, face often spared[2,4]	Pruritus, burning[4]	Delayed-type hypersensitivity reaction[2]
Solar Urticaria	Several minutes after UV exposure[18]	Resolves within 30 minutes to 24 hours after sun removal[18]	Urticaria, wheals, erythema[18]	Sun-exposed areas[18]	Pruritus , burning, systemic symptoms in approximately 10% of cases ie, nausea, headache[18]	Immunoglobulin E (IgE)-mediated mast cell activation in response to UVR[18]
Photoallergic Dermatitis	Hours to days after exposure to photosensitizer and UVR[19]	Days to weeks[20]	Eczematous dermatitis[19]	Sun-exposed areas[19]	History of topical photosensitizer[19]	Type IV hypersensitivity reaction[20]
Cutaneous Porphyria	Variable/chronic photosensitivity[21]	Weeks to months[21]	Blisters, erosions, scarring[21]	Sun-exposed areas; particularly hands and face[21]	Red/brown urine discoloration[21]	Porphyrin accumulation causing photosensitivity[21]

evidence base with human clinical trials demonstrating its role in photoprotection.[1,10,11] PLE exerts anti-inflammatory and antioxidant effects that counteract UV-induced damage, as it has been shown to increase the minimal erythema dose and reduce erythema intensity after a five-day course of PLE 250 mg twice daily.[1,9,10] It was also highlighted as an adjunct for actinic prurigo, demonstrating reduced disease severity and duration after one month of treatment at 15 mg/kg/day.[9] Additionally, antioxidant formulations containing vitamins C and E, ferulic acid, phenolics, or nanoformulated cannabidiol can reduce oxidative stress.[12,13,14] Topical cannabidiol has also been demonstrated to prevent UV-A-induced nuclear and mitochondrial DNA mutations.[14]

Treatment

Traditional treatment includes corticosteroids, phototherapy, discontinuation of offending agents, and treatment of underlying causes.[15] Topical or systemic corticosteroids may expedite resolution, while photohardening with UVB phototherapy, typically administered three to five times per week for 15–20 sessions, can promote light desensitization in advanced cases.[15] Additionally, thalidomide and hydroxychloroquine have long been used off-label for actinic prurigo, polymorphous light eruption, and solar urticaria.[1,16] In one report, thalidomide cleared pediatric actinic prurigo after seven weeks at 3 mg/kg/day.[1] Additionally, a multicenter study in Korea reported an 88.7% (n = 196/221) response rate in patients with unspecified photodermatitis after a median treatment of two weeks with hydroxychloroquine 200 or 400 mg daily.[16]

Biologics have been reported as emerging treatments for photodermatoses, although supporting studies are limited.[1] Omalizumab, an anti-IgE monoclonal antibody, has promoted remission in solar urticaria after four treatment courses of 375 mg every two weeks for six months, followed by 150 mg once monthly for three months.[1] Additionally, dupilumab, an interleukin (IL)-4 receptor antagonist, has been reported to achieve clearance of pediatric actinic prurigo after 8 weeks with 200 mg administered every two weeks, as well as adult actinic dermatosis after 12-16 weeks with 300 mg every two weeks.[1]

For erythropoietic protoporphyria, the US Food and Drug Administration (FDA) has approved subcutaneous afamelanotide, an α-melanocyte-stimulating hormone (α-MSH) analog, to extend the duration of time spent in direct sunlight without pain.[1,17] Afamelanotide induces skin pigmentation, enhances DNA repair, and promotes antioxidant defenses.[1,17] It has also been proposed as a potential therapy for idiopathic polymorphic light eruption; however, it has not yet been approved by the FDA for this indication.[8]

CONCLUSION

In the absence of established treatment guidelines, growing evidence supports a shift in the management of photodermatoses toward more personalized, multimodal approaches. Recent advances in photoprotective formulations, biologics, and oral supplements have broadened available therapeutic and preventive options for photodermatoses, enabling treatment to be tailored to patient comfort and preferences.

DISCLOSURES

MF's work is funded through independent research grants from Incyte and Johnson & Johnson. NZ's work is funded through an independent research grant from Galderma. NL and AF have no conflicts to disclose.

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doi:10.36849/JDD.9361e

March 2026 e40 Volume 25 • Issue 3

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Topical Ruxolitinib Therapy Decreases Rates of Depression and Anxiety: A Retrospective Analysis in Vitiligo Patients

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To the Editor,

Vitiligo, a chronic autoimmune condition characterized by loss of melanocytes and resultant skin depigmentation, is associated with reduced quality of life, and increased risks of psychiatric comorbidities such as depression and anxiety.[1-3] While current clinical assessments focus on improving objective markers of disease burden, such as percentage of Body Surface Area (BSA), little is known about the effect of vitiligo treatment on other patient outcomes like depression and anxiety.

Ruxolitinib, a topical Janus kinase (JAK) inhibitor, is a novel and effective therapy approved for repigmentation in non-segmental vitiligo.[3] Despite its growing use, its potential impact on depression and anxiety rates in treated patients has not yet been reported.

In this retrospective cohort study, we used the TriNetX Network to examine rates of depression and anxiety in vitiligo patients treated with ruxolitinib. The TriNetX Network allows examination of claims and electronic health record data for patients from 24 US healthcare organizations. This type of claims-level analysis offers, among its advantages, the ability to evaluate large numbers of patients, to associate different clinical states in each patient (via ICD codes), and to evaluate interventions via pharmacy claims data.

TABLE 1.

Risk of Depression and Anxiety Disorders in Patients with Vitiligo Treated with Ruxolitinib Compared to Those Not Treated with Ruxolitinib

Outcome	Cohort	Patients in Cohort	Patients with Outcome	Risk (%)	Risk Ratio	95% CI	*P*-Value
6-month time window							
Anxiety Disorder	JAKi + Vitiligo	4,166	38	0.90%	0.675	(0.449, 1.013)	0.056
	Control	4,289	58	1.40%			
Depression	JAKi + Vitiligo	4,291	27	0.60%	0.49	(0.310, 0.775)	0.002
	Control	4,284	55	1.30%			
1-year time window							
Anxiety Disorder	JAKi + Vitiligo	4,640	48	1.03%	0.66	(0.504, 0.865)	0.002
	Control	4,725	55	1.16%			
Depression	JAKi + Vitiligo	4,379	76	1.73%	0.553	(0.406, 0.752)	0
	Control	4,436	155	3.49%			
18-month time window							
Anxiety Disorder	JAKi + Vitiligo	4,166	84	2.00%	0.675	(0.543, 1.419)	0.59
	Control	4,289	131	3.10%			
Depression	JAKi + Vitiligo	4,291	62	1.40%	0.49	(0.332, 0.667)	0
	Control	4,284	112	2.60%			
2-year time window							
Anxiety Disorder	JAKi + Vitiligo	4,640	31	0.67%	0.876	(0.543, 1.419)	0.59
	Control	4,725	36	0.76%			
Depression	JAKi + Vitiligo	4,379	50	1.14%	0.478	(0.332, 0.667)	0
	Control	4,436	106	2.39%			

doi:10.36849/JDD.9361e

March 2026 e41 Volume 25 • Issue 3

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Journal of Drugs in Dermatology

Vitiligo patients treated with ruxolitinib were matched 1:1 to vitiligo patients not treated with ruxolitinib using a greedy nearest neighbor algorithm based on age, sex, and race/ethnicity. All patients with a history of depression (ICD-10: F32) or anxiety disorder (ICD-10: F41.9) prior to vitiligo diagnosis were excluded. Matching yielded two otherwise similar cohorts (all p-values for age, sex, race/ethnicity were greater than 0.05). Concurrent use of other treatments was allowed in both groups. Presence of new depression and anxiety diagnoses was measured at 6, 12, 18, and 24 months after patient enrollment.

Compared to matched controls, ruxolitinib-treated patients had a significantly lower rate of depression at all measured timepoints (range: 44.7 – 52.2%; Table 1). Anxiety disorder risk also trended lower in the Ruxolitinib group, but only reached statistical significance at the 18 month timepoint, suggesting a less consistent relationship compared to depression outcomes. Ruxolitinib inhibits JAK1 and JAK2, core enzymes in the JAK-STAT signaling pathway that regulate inflammatory and immune responses. In vitiligo, aberrant activation of this pathway leads to the recruitment of CXCR3+ CD8+ T cells, which selectively destroy melanocytes. Ruxolitinib disrupts this mechanism, thereby allowing repigmentation to occur.[1,2]

In conclusion, topical ruxolitinib is associated with a reduction in depression rates among vitiligo patients, with improvement observed across all time points evaluated (6, 12, 18, and 24 months). Anxiety risk showed a downward trend and reached significance only at 18 months posttreatment.These findings can assist physicians in considering ruxolitinib for vitiligo patients at risk for mood disorders such as depression and may also inform insurance coverage decisions and enhance patient compliance. Limitations include the study's retrospective design, reliance on ICD codes from electronic health records, and potential unmeasured confounding despite propensity score matching. Future research should prospectively assess the psychiatric effects of vitiligo treatments using validated mental health measures and investigate whether JAK inhibitors have direct neuroprotective or mood-stabilizing properties.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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