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JOURNAL OF DRUGS IN DERMATOLOGY

# JDD

DRUGS • DEVICES • METHODS



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Psoriatic Arthritis Progression With JAK Inhibitors

Generative Artificial Intelligence for Acne Remission Maintenance

40-Gene Expression Profiling in Cutaneous Squamous Cell Carcinoma

Peptides for Hair Growth and Alopecia

Impetigo Antibiotic Stewardship and Treatment Alternatives

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ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

ZORYVE®
(roflumilast)

*Inflammatory dermatoses?*

# ZORYVE® IT RELIEVE IT

The ***power*** and ***versatility*** to be your go-to topical.[1,2]




Delivers **powerful results** head to toe[1,2*]

**Safe** and **well tolerated** with no limitations on duration of use or percent BSA[1,2]

**MILD TO MODERATE**
**ATOPIC DERMATITIS**
**Cream 0.05%** for age 2–5
**Cream 0.15%** for age 6+

**Atopic dermatitis:** 31% of patients achieved vIGA-AD Success at Week 4 with ZORYVE cream 0.15% (n=884) vs 14% with vehicle (n=453). 25% of patients achieved vIGA-AD Success at Week 4 with ZORYVE cream 0.05% (n=436) vs 11% with vehicle (n=215).[1,3,4]

**Plaque psoriasis:** 40% of patients achieved IGA Success at Week 8 with ZORYVE cream 0.3% (n=576) vs 7% with vehicle (n=305). 63% of patients achieved S-IGA Success at Week 8 with ZORYVE foam 0.3% (n=481) vs 21% with vehicle (n=255). In ARRECTOR, 46% of patients achieved B-IGA Success at Week 8 with ZORYVE foam (n=281) vs 20% with vehicle (n=151).[1,2,5-7]

**Seborrheic dermatitis:** 77% of patients achieved IGA Success at Week 8 with ZORYVE foam 0.3% (n=458) vs 53% with vehicle (n=225).[2,6]

**INDICATIONS**

ZORYVE cream, 0.05%, is indicated for topical treatment of mild to moderate atopic dermatitis in pediatric patients 2 to 5 years of age.

ZORYVE cream, 0.15%, is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.

ZORYVE cream, 0.3%, is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in adult and pediatric patients 2 years of age and older.

ZORYVE topical foam, 0.3%, is indicated for the treatment of plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older.

**INDICATIONS** (continued)

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

**IMPORTANT SAFETY INFORMATION**

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

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

The most common adverse reactions reported (≥1%) for ZORYVE cream 0.05% for pediatric patients with atopic dermatitis 2 to 5 years of age were upper respiratory tract infection (4.1%), diarrhea (2.5%), vomiting (2.1%), rhinitis (1.6%), conjunctivitis (1.4%), and headache (1.1%).

The most common adverse reactions reported (≥1%) for ZORYVE cream 0.15% for patients with atopic dermatitis 6 years of age or older were headache (2.9%), nausea (1.9%), application site pain (1.5%), diarrhea (1.5%), and vomiting (1.5%).

The most common adverse reactions reported (≥1%) for ZORYVE cream 0.3% for plaque psoriasis were diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%).

The most common adverse reactions reported (≥1%) for ZORYVE foam 0.3% for plaque psoriasis were headache (3.1%), diarrhea (2.5%), nausea (1.7%), and nasopharyngitis (1.3%).

Not a steroid[1,2]

No boxed warning

NOW AVAILABLE

DOWN TO AGE 2




## Start and Stay with ZORYVE

Continuous care for chronic conditions[1,2]

**Discover more:**
**ZORYVEHCP.com**

SIMPLE, ***ONCE-DAILY*** TREATMENT[1,2]

### PLAQUE PSORIASIS

**Cream 0.3%** for age 2+
**Foam 0.3%** for age 12+

### SEBORRHEIC DERMATITIS

**Foam 0.3%** for age 9+

**IMPORTANT SAFETY INFORMATION** (continued)

The most common adverse reactions reported (≥1%) for ZORYVE foam 0.3% for seborrheic dermatitis were nasopharyngitis (1.5%), nausea (1.3%), and headache (1.1%).

**Please see accompanying Brief Summary of the full Prescribing Information for ZORYVE cream and full Prescribing Information for ZORYVE foam.**

**STUDY DESIGNS**

**Atopic Dermatitis Cream 0.05%:** A Phase 3, multicenter, randomized, double-blind, vehicle-controlled study (INTEGUMENT-PED) evaluated 652 participants with mild to moderate atopic dermatitis ages 2–5. Caregivers applied ZORYVE cream 0.05% or vehicle to patients once daily for 4 weeks. ZORYVE cream = 436, vehicle = 215. Primary endpoint was vIGA-AD Success at Week 4.[1,4]

**Atopic Dermatitis Cream 0.15%:** Two Phase 3, multicenter, randomized, double-blind, vehicle-controlled studies (INTEGUMENT-1 and INTEGUMENT-2) evaluated 1337 participants with mild to moderate atopic dermatitis ages 6 years and older. Participants applied ZORYVE cream 0.15% or vehicle once daily for 4 weeks. ZORYVE cream = 884, vehicle = 453. Primary endpoint was vIGA-AD Success at Week 4.[1,3]

**Plaque Psoriasis Cream:** Two Phase 3, multicenter, randomized, parallel, double-blind, vehicle-controlled studies (DERMIS-1 and DERMIS-2) evaluated 881 participants with plaque psoriasis treated with ZORYVE cream 0.3% or vehicle once daily for 8 weeks. ZORYVE = 576, vehicle = 305. Primary endpoint was IGA Success at Week 8.[1,8]

**Plaque Psoriasis Foam:** Two multicenter, randomized, parallel, double-blind, vehicle-controlled studies (ARRECTOR and Trial 204) evaluated 736 participants with plaque psoriasis treated with ZORYVE foam 0.3% or vehicle once daily for 8 weeks. ZORYVE = 481, vehicle = 255. Primary endpoints were S-IGA Success at Week 8 in both studies, and B-IGA Success at Week 8 in ARRECTOR.[2,7,9]

**Seborrheic Dermatitis Foam:** Two multicenter, randomized, double-blind, vehicle-controlled studies (STRATUM and Trial 203) evaluated 683 participants with moderate to severe seborrheic dermatitis treated with ZORYVE foam 0.3% or vehicle once daily for 8 weeks. ZORYVE = 458, vehicle = 225. Primary endpoint was IGA Success at Week 8.[2,10]

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

B-IGA=Body Investigator Global Assessment; B-IGA/IGA/S-IGA/vIGA-AD Success=Achievement of Clear (0) or Almost Clear (1) and a ≥2-grade improvement from baseline; BSA=Body Surface Area; IGA=Investigator Global Assessment; S-IGA=Scalp Investigator Global Assessment; vIGA-AD=validated Investigator Global Assessment-Atopic Dermatitis.

**References: 1.** ZORYVE® (roflumilast) cream. Prescribing information. Arcutis Biotherapeutics, Inc; 2026. **2.** ZORYVE® (roflumilast) foam. Prescribing information. Arcutis Biotherapeutics, Inc; 2025. **3.** Simpson E, Boguniewicz M, Eichenfield L, et al. Pooled efficacy, patient reported outcomes, and safety of roflumilast cream 0.15% from the INTEGUMENT-1 and INTEGUMENT-2 phase 3 clinical trials of adults and children with atopic dermatitis. Poster presented at: American Academy of Dermatology Annual Meeting; March 8–12, 2024; San Diego, CA. **4.** Eichenfield LF, Serrao R, Prajapati VH, et al. Efficacy and safety of once-daily roflumilast cream 0.05% in pediatric patients aged 2–5 years with mild-to-moderate atopic dermatitis (INTEGUMENT-PED): a phase 3 randomized controlled trial. *Pediatr Dermatol*. 2025;42(2):296–304. doi:10.1111/pde.15840 **5.** Lebwohl M, Gooderham MJ, Guenthner ST, et al. Poster presented at: American Academy of Dermatology Annual Meeting; March 25-29, 2022; Boston, MA. **6.** Data on File. Arcutis Biotherapeutics, Inc. **7.** Gooderham M, Alonso-Llamazares J, Bagel J, et al. Roflumilast foam, 0.3%, for psoriasis of the scalp and body: the ARRECTOR phase 3 randomized clinical trial. *JAMA Dermatol*. 2025;161(7):698-706. doi:10.1001/jamadermatol.2025.1136 **8.** Lebwohl M, Kircik L, Moore A, et al. Effect of roflumilast cream vs vehicle cream on chronic plaque psoriasis: the DERMIS-1 and DERMIS-2 randomized clinical trials. *JAMA*. 2022;328(11):1073–1084. **9.** Kircik LH, Alonso-Llamazares J, Bhatia N, et al. Once-daily roflumilast foam 0.3% for scalp and body psoriasis: a randomized, double-blind, vehicle-controlled phase IIb study. *Br J Dermatol*. 2023;189(4):392–399. doi:10.1093/bjd/ljad182 **10.** Blauvelt A, Draelos Z, Stein Gold L, et al. Roflumilast foam 0.3% for adolescent and adult patients with seborrheic dermatitis: A randomized, double-blinded, vehicle-controlled, phase 3 trial. *J Am Acad Dermatol*. 2024 May;90(5):986–993. doi:10.1016/j.jaad.2023.12.065

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ARCUTIS® BIOTHERAPEUTICS

**Brief Summary of Prescribing Information for ZORYVE® (roflumilast) cream, 0.15%, ZORYVE® (roflumilast) cream, 0.3%, ZORYVE® (roflumilast) cream, 0.05%, and ZORYVE® (roflumilast) foam, 0.3%, for topical use. See package insert for full Prescribing Information.**

**INDICATIONS AND USAGE**

ZORYVE cream, 0.3%, is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in adult and pediatric patients 2 years of age and older.

ZORYVE cream, 0.15%, is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.

ZORYVE cream, 0.05%, is indicated for topical treatment of mild to moderate atopic dermatitis in pediatric patients 2 to 5 years of age.

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

ZORYVE topical foam, 0.3%, is indicated for the treatment of plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older.

**DOSAGE AND ADMINISTRATION**

Use ZORYVE cream, 0.3%, for the treatment of plaque psoriasis.

Use ZORYVE cream, 0.15%, for the treatment of mild to moderate atopic dermatitis.

Use ZORYVE cream, 0.05%, for the treatment of mild to moderate atopic dermatitis in patients 2 to 5 years of age.

Apply ZORYVE cream to affected areas once daily and rub in completely. Wash hands after application.

Use ZORYVE foam, 0.3%, for the treatment of seborrheic dermatitis and plaque psoriasis of the scalp and body.

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

Wash hands after application.

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

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

**CONTRAINDICATIONS**

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

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

Plaque Psoriasis (ZORYVE cream, 0.3%)

In two multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2), 881 adult and pediatric subjects 6 years of age or older with plaque psoriasis were treated with ZORYVE cream, 0.3%, or vehicle cream once daily for 8 weeks.

The proportion of subjects who discontinued treatment due to an adverse reaction was 1.0% for subjects treated with ZORYVE cream, 0.3%, and 1.3% for subjects treated with vehicle cream. The most common adverse reaction that led to discontinuation of ZORYVE cream, 0.3%, was application site urticaria (0.3%).

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE cream, 0.3%, and for which the rate exceeded the rate for vehicle cream.

**Table 1: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 6 Years of Age and Older with Plaque Psoriasis Treated with ZORYVE Cream, 0.3%, (and More Frequently than Vehicle Cream) for 8 Weeks in Trials DERMIS-1 and DERMIS-2**

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

In 644 subjects with plaque psoriasis who continued treatment with ZORYVE cream, 0.3%, for up to 64 weeks in open-label extension trials, the adverse reaction profile was consistent with that observed in vehicle-controlled trials.

The safety of ZORYVE cream, 0.3%, once daily was assessed in an open-label trial for up to 24 weeks. The adverse reaction profile in pediatric subjects aged 2 years to 5 years of age was consistent with that observed in adult and pediatric subjects 6 years of age and older.

Plaque Psoriasis (ZORYVE foam, 0.3%)

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 204 and ARRECTOR), 734 adult and pediatric subjects 12 years of age and older with plaque psoriasis of the scalp and body were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks.

Table 2 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE foam, 0.3%.

**Table 2: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 12 Years of Age and Older with Plaque Psoriasis of the Scalp and Body Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 204 and Trial ARRECTOR**

| Adverse Reaction | ZORYVE Foam, 0.3% (N=479) n (%) | Vehicle Foam (N=225) n (%) |
|---|---|---|
| Headache | 15 (3.1) | 3 (1.2) |
| Diarrhea | 12 (2.5) | 4 (1.6) |
| Nausea | 8 (1.7) | 0 (0) |
| Nasopharyngitis | 6 (1.3) | 2 (0.8) |

The following additional adverse reaction was reported in fewer than 1% of subjects treated with ZORYVE foam, 0.3%: insomnia.

The adverse reaction profile in pediatric subjects was consistent with that observed in adults.

Atopic Dermatitis

*Adult and Pediatric Subjects 6 Years of Age and Older*

In two multicenter, randomized, double-blind, vehicle-controlled trials (INTEGUMENT-1 and INTEGUMENT-2), 1336 adult and pediatric subjects 6 years of age or older with mild to moderate atopic dermatitis were treated with ZORYVE cream, 0.15%, or vehicle cream once daily for 4 weeks.

The proportion of subjects who discontinued treatment due to an adverse reaction was 1.6% for subjects treated with ZORYVE cream, 0.15%, and 1.1% for subjects treated with vehicle cream.

Table 3 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE cream, 0.15%, and for which the rate exceeded the rate for vehicle cream.

**Table 3: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 6 Years of Age and Older with Atopic Dermatitis Treated with ZORYVE Cream, 0.15%, (and More Frequently than Vehicle Cream) for 4 Weeks in Trials INTEGUMENT-1 and INTEGUMENT-2**

| Adverse Reaction | ZORYVE Cream, 0.15% (N=885) n (%) | Vehicle Cream (N=451) n (%) |
|---|---|---|
| Headache | 26 (2.9) | 4 (0.9) |
| Nausea | 17 (1.9) | 2 (0.4) |
| Application site pain | 13 (1.5) | 3 (0.7) |
| Diarrhea | 13 (1.5) | 2 (0.4) |
| Vomiting | 13 (1.5) | 2 (0.4) |

The adverse reaction of insomnia was reported in fewer than 1% of subjects treated with ZORYVE cream, 0.15%.

*Pediatric Subjects 2 to 5 Years of Age*

In a multicenter, randomized, double-blind, vehicle-controlled trial (INTEGUMENT-PED), 652 pediatric subjects 2 to 5 years of age with mild to moderate atopic dermatitis were treated with ZORYVE cream, 0.05%, or vehicle cream once daily for 4 weeks.

Table 4 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE cream, 0.05%, and for which the rate exceeded the rate for vehicle cream.

**Table 4: Adverse Reactions Reported in ≥1% of Pediatric Subjects 2 to 5 Years of Age with Atopic Dermatitis Treated with ZORYVE Cream, 0.05%, (and More Frequently than Vehicle) for 4 Weeks in Trial INTEGUMENT-PED**

| Adverse Reaction | ZORYVE Cream, 0.05% (N=437) n (%) | Vehicle Cream (N=215) n (%) |
|---|---|---|
| Upper respiratory tract infection | 18 (4.1) | 3 (1.4) |
| Diarrhea | 11 (2.5) | 1 (0.5) |
| Vomiting | 9 (2.1) | 0 |
| Rhinitis | 7 (1.6) | 0 |
| Conjunctivitis | 6 (1.4) | 0 |
| Headache | 5 (1.1) | 0 |

*Adult and Pediatric Subjects 2 Years of Age and Older*

The long-term safety of ZORYVE cream, 0.15%, and ZORYVE cream, 0.05%, was assessed in an open-label extension trial of 1219 subjects 2 years of age and older with mild to moderate atopic dermatitis who had completed one of the 4-week vehicle-controlled trials. The safety profile observed in the open-label extension trial was generally consistent with the safety profile observed at Week 4.

Seborrheic Dermatitis (ZORYVE foam, 0.3%)

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 203 and STRATUM), 683 adult and pediatric subjects 9 years of age or older with seborrheic dermatitis were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks.

Table 5 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE foam, 0.3%.

**Table 5: Adverse Reactions Reported in ≥1% of Adult and Pediatric Subjects 9 Years of Age and Older with Seborrheic Dermatitis Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 203 and Trial STRATUM**

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

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

The adverse reaction profile in pediatric subjects was consistent with that observed in adults.

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

There are insufficient data available on the use of ZORYVE in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 36 and 31 times the maximum recommended human dose (MRHD), respectively, for ZORYVE cream and up to 21 and 18 times the MRHD, respectively, for ZORYVE foam. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 12 times the MRHD for ZORYVE cream and 7 times the MRHD for ZORYVE foam. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 19 and 59 times the MRHD, respectively, for ZORYVE cream and 11 and 34 times the MRHD, respectively, for ZORYVE foam. Roflumilast has been shown to adversely affect pup post-natal

development when dams were treated with an oral dose 59 times the MRHD for ZORYVE cream and 34 times the MRHD for ZORYVE foam during pregnancy and lactation periods in mice.

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

Clinical Considerations

*Labor and delivery*

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

Data

*Animal data*

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (36 times the MRHD for ZORYVE cream and 21 times the MRHD for ZORYVE foam on a mg/m$^2$ basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (4 times the MRHD for ZORYVE cream and 2 times the MRHD for ZORYVE foam on a mg/m$^2$ basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (12 times the MRHD for ZORYVE cream and 7 times the MRHD for ZORYVE foam on a mg/m$^2$ basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (35 times the MRHD for ZORYVE cream and 20 times the MRHD for ZORYVE foam on a mg/m$^2$ basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (31 times the MRHD for ZORYVE cream and 18 times the MRHD for ZORYVE foam on a mg/m$^2$ basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (19 and 59 times the MRHD, respectively, for ZORYVE cream and 11 and 34 times the MRHD, respectively, for ZORYVE foam on a mg/m$^2$ basis). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (19 times the MRHD for ZORYVE cream and 11 times the MRHD for ZORYVE foam on a mg/m$^2$ basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (59 times the MRHD for ZORYVE cream and 34 times the MRHD for ZORYVE foam on a mg/m$^2$ basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (116 times the MRHD for ZORYVE cream and 68 times the MRHD for ZORYVE foam on a mg/m$^2$ basis).

**Lactation**

Risk Summary

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

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

Clinical Considerations

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

Data

*Animal data*

Plaque Psoriasis (ZORYVE cream, 0.3%) and Atopic Dermatitis (ZORYVE cream, 0.15%)

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively. The concentration of roflumilast in animal milk does not necessarily predict the concentration of drug in human milk.

Plaque Psoriasis and Seborrheic Dermatitis (ZORYVE foam, 0.3%)

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively. The concentration of roflumilast in animal milk does not necessarily predict the concentration of drug in human milk.

**Females and Males of Reproductive Potential**

Fertility

Plaque Psoriasis (ZORYVE cream and ZORYVE foam) and Atopic Dermatitis (ZORYVE cream)

In a human spermatogenesis study, oral roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period.

**Pediatric Use**

Plaque Psoriasis (ZORYVE cream, 0.3%)

The safety and effectiveness of ZORYVE cream, 0.3%, for the topical treatment of plaque psoriasis, including intertriginous areas, have been established in pediatric patients 2 years of age and older. Use of ZORYVE cream, 0.3%, in pediatric patients 2 years of age and older is supported by data from two 8-week, vehicle-controlled, safety and efficacy trials which included 18 subjects 6 to 17 years of age, of whom 11 received ZORYVE cream, 0.3%; one open-label, safety trial in 21 pediatric subjects 2 to 5 years of age with up to 25% BSA involvement who applied ZORYVE cream, 0.3%, up to 24 weeks. Additional safety and pharmacokinetic (PK) data supported this use: open-label trials of 2- and 24-weeks duration which included 25 subjects 12 to 17 years of age treated with ZORYVE cream, 0.3%; two 4-week, open-label, safety and PK studies which included 20 pediatric subjects 6 to 11 years of age and 10 pediatric subjects 2 to 5 years of age, treated with ZORYVE cream, 0.3%.

The safety and effectiveness of ZORYVE cream, 0.3%, have not been established in pediatric patients younger than 2 years of age.

Plaque Psoriasis (ZORYVE foam, 0.3%)

The safety and effectiveness of ZORYVE topical foam, 0.3%, for the treatment of plaque psoriasis of the scalp and body have been established in pediatric patients 12 years of age and older. Use of ZORYVE foam, 0.3%, in this age group is supported by data from two 8-week, vehicle-controlled trials which included 12 subjects 12 to 17 years of age, of whom 8 received ZORYVE foam, 0.3%. Use of ZORYVE foam, 0.3%, in pediatric patients 12 years of age and older is also supported by data from an open-label trial of 8 weeks duration which included 7 subjects 12 to 17 years of age treated with ZORYVE foam, 0.3%.

The safety and effectiveness of ZORYVE foam, 0.3%, in pediatric patients below the age of 12 years with plaque psoriasis have not been established.

Atopic Dermatitis (ZORYVE cream, 0.15%)

The safety and effectiveness of ZORYVE cream, 0.15%, for the topical treatment of mild to moderate atopic dermatitis have been established in pediatric patients 6 years of age and older. Use of ZORYVE cream, 0.15%, in this age group is supported by data from two 4-week, vehicle-controlled, safety and efficacy trials which included 615 subjects 6 to 17 years of age, of whom 406 received ZORYVE cream, 0.15%. Use of ZORYVE cream, 0.15%, in pediatric patients 6 years of age and older is also supported by data from 481 pediatric subjects treated with ZORYVE cream, 0.15%, in open-label trials, of which 104 were treated for 52 weeks.

In an open-label PK trial in 36 pediatric subjects 2 to 16 years of age, following topical administration of roflumilast cream, 0.15%, once daily for 2 weeks, mean systemic exposure of roflumilast and roflumilast N-oxide in subjects 2 to 5 years of age was approximately 3.2-fold and 5.2-fold higher, respectively, compared to subjects 12 to 16 years of age, and approximately 2-fold and 2.3-fold higher, respectively, compared to subjects 6 to 11 years of age.

The safety and effectiveness of ZORYVE cream, 0.15%, have not been established in pediatric patients younger than 6 years of age.

Atopic Dermatitis (ZORYVE cream, 0.05%)

The safety and effectiveness of ZORYVE cream, 0.05%, for the topical treatment of mild to moderate atopic dermatitis have been established in pediatric patients 2 to 5 years of age. Use of ZORYVE cream, 0.05%, in this age group is supported by data from one 4-week, vehicle-controlled, safety and efficacy trial which included 652 subjects 2 to 5 years of age, of whom 437 received ZORYVE cream, 0.05%. Use of ZORYVE cream, 0.05%, in pediatric patients 2 to 5 years of age is also supported by data from 572 pediatric subjects treated with ZORYVE cream, 0.05%, in open-label trials, of whom 353 were treated for 52 weeks.

The safety and effectiveness of ZORYVE cream, 0.05%, have not been established in pediatric patients younger than 2 years of age and older than 6 years of age.

Seborrheic Dermatitis (ZORYVE foam, 0.3%)

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

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

**Geriatric Use**

There were 184 patients 65 years of age and older in clinical studies for plaque psoriasis and atopic dermatitis.

Plaque Psoriasis (ZORYVE cream, 0.3%)

Of the 576 patients treated with ZORYVE cream, 0.3%, in the 2 controlled clinical studies for plaque psoriasis, 56 (9.7%) were 65 to 74 years of age and 21 (3.7%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plaque Psoriasis (ZORYVE foam, 0.3%)

Of the 734 subjects with plaque psoriasis of the scalp and body exposed to ZORYVE foam, 0.3%, or vehicle for up to 8 weeks in the controlled clinical trials, 82 (11%) were 65 years of age or older, and 21 (3%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Atopic Dermatitis (ZORYVE cream, 0.15%)

Of the 885 patients treated with ZORYVE cream, 0.15%, in the 2 controlled clinical studies for atopic dermatitis, 36 (4.1%) were 65 to 74 years of age and 8 (0.9%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Seborrheic Dermatitis (ZORYVE foam, 0.3%)

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

**Hepatic Impairment**

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

**PATIENT COUNSELING INFORMATION**

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

Administration Instructions

Advise patients or caregivers that ZORYVE foam and ZORYVE cream are for topical use only and are not for ophthalmic, oral, or intravaginal use.

Instruct patients or caregivers to shake the can of ZORYVE foam, 0.3%, prior to each use.

Instruct patients or caregivers to wash hands after applying ZORYVE foam or ZORYVE cream.

Flammability

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

Lactation

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

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Progression to Psoriatic Arthritis Among Psoriasis Patients Treated With JAK Inhibitors Compared With IL-17/23 Inhibitors

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## ABSTRACT

**Background:** Psoriasis is a chronic immune-mediated inflammatory disease that may progress to psoriatic arthritis (PsA). Although multiple systemic therapies are available, including interleukin (IL)-17 and IL-23 inhibitors and Janus kinase (JAK) inhibitors, their comparative associations with incident PsA remain incompletely characterized.

**Methods:** We performed 2 retrospective, propensity score-matched cohort studies within a large federated research network using a TARGET trial emulation framework. Adults with psoriasis initiating a JAK inhibitor were separately compared with those initiating an IL-17 inhibitor or an IL-23 inhibitor; patients with preexisting PsA were excluded. Cohorts were matched 1:1 on demographics, race and ethnicity, comorbidities, psoriasis subtype, baseline musculoskeletal symptoms, prior medication exposure, and healthcare utilization. Balance was assessed using standardized mean differences ($P$<0.10). The primary outcome was incident PsA (L40.5) occurring 1 day to 5 years after treatment initiation. Risk ratios (RRs) with 95% confidence intervals (CIs) and time-to-event analyses using Cox models and Kaplan-Meier methods were applied.

**Results:** PsA incidence was 15.1% with IL-23 inhibitors vs 19.0% with JAK inhibitors (RR 1.25, 95% CI 1.15-1.37; HR 1.32, 95% CI 1.20-1.46; log-rank $P$<0.0001). In contrast, IL-17 inhibitors were associated with a higher incidence than JAK inhibitors (27.1% vs 16.8%; RR 0.62, 95% CI 0.58-0.67; HR 0.66, 95% CI 0.61-0.72; log-rank $P$<0.0001).

**Conclusion:** IL-23 inhibitors were associated with the lowest observed incidence of PsA. Although causal inference is limited, these findings may help inform therapeutic decision-making in psoriasis.

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## INTRODUCTION

Psoriatic arthritis (PsA) is a debilitating inflammatory arthropathy and a major long-term complication of psoriasis, affecting up to 30% of patients.[1] Although the mechanistic link between cutaneous psoriasis and PsA is not fully elucidated, both conditions are mediated by dysregulated immune signaling, prominently involving the IL-23/IL-17 axis and downstream proinflammatory cytokines.[2] Emerging evidence suggests that systemic therapies for psoriasis may differentially influence the subsequent development of PsA, underscoring the clinical importance of treatment selection in patients at risk.[3-5]

Psoriasis is a chronic immune-mediated inflammatory disease driven by adaptive immune pathways, particularly those involving IL-23 and IL-17.[2,6] IL-23 signaling activates the tyrosine kinases JAK2 and TYK2, leading to STAT3 phosphorylation and induction of the transcription factor RORγt, which promotes Th17 cell differentiation and IL-17 cytokine production.[7-10] IL-17 and IL-23 inhibitors have become cornerstone therapies for moderate-to-severe psoriasis, while JAK inhibitors represent an additional systemic option.[1,11] Notably, JAK inhibitors are also widely used in inflammatory joint diseases, raising the possibility that they may confer benefit in preventing or delaying PsA, albeit with potentially less robust cutaneous efficacy.[12] In current clinical practice, JAK inhibitors are typically reserved after inadequate response or intolerance to conventional disease-modifying antirheumatic drugs.[13]

Determining how different systemic therapies influence the risk of developing PsA is essential for optimizing psoriasis management. While prior studies have examined to a degree the comparative efficacy of IL-17 and IL-23 inhibitors, the relative impact on PsA risk remains poorly characterized.[1,11,14] To address this knowledge gap, we conducted a retrospective 5-year outcomes study evaluating incident PsA among patients

with psoriasis treated with JAK inhibitors compared with IL-17 and IL-23 inhibitors, leveraging a large real-world dataset to enhance statistical power and clinical relevance.

## MATERIALS AND METHODS

### Study Design and Data Source

We conducted a retrospective cohort study using a target trial emulation framework to evaluate the association between initiation of Janus kinase (JAK) inhibitors and the risk of incident psoriatic arthritis (PsA), compared with initiation of interleukin (IL)-17 and IL-23 inhibitors among patients with psoriasis. The observational emulation was designed to mirror a hypothetical randomized controlled trial as closely as possible. Diagnoses were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes, and medication exposures were identified using RxNorm and Anatomical Therapeutic Chemical (ATC) classifications.

### Study Population and Eligibility Criteria

Eligible individuals were adults with a diagnosis of psoriasis, defined by at least 1 ICD-10 code for psoriasis (L40.0 or L40.9), and no prior diagnosis of psoriatic arthritis. Patients were required to initiate a study drug during the study period and have complete baseline demographic and clinical covariate data. Patients were excluded if they had evidence of the primary outcome (PsA) or any prespecified sensitivity or negative control outcome prior to the index date. Individuals with missing demographic or covariate data required for propensity score modeling were also excluded.

### Exposure Cohorts and Index Date

Patients were classified into mutually exclusive exposure cohorts based on the first eligible prescription during the study period. Three cohorts were defined:

1. JAK inhibitor initiators, defined as patients with PsO who initiated a JAK inhibitor and had no prior use of a JAK inhibitor before the start of the study.
2. IL-23 inhibitor initiators, defined as patients with psoriasis who initiated an IL-23 inhibitor with no prior IL-23 inhibitor use.
3. IL-17 inhibitor initiators, defined as patients with psoriasis who initiated an IL-17 inhibitor with no prior IL-17 inhibitor use.

The index date was defined as the date of the first qualifying prescription for the respective therapy. Follow-up began 1 day after the index date to minimize immortal time bias.

### Target Trial Emulation Framework

A target trial is a conceptual framework used in observational research to explicitly specify the design of a hypothetical randomized controlled trial that would ideally answer the causal question of interest. Key components of the target trial include eligibility criteria, treatment strategies, treatment assignment, start of follow-up (time zero), outcomes, estimates, and analytic approach. By clearly defining these elements in advance, the target trial framework helps prevent common sources of bias in observational studies, such as immortal time bias, selection bias, and inappropriate adjustment for posttreatment variables. Observational data are then analyzed to emulate this hypothetical trial as closely as possible, using methods such as propensity score-based adjustment to approximate randomization and intention-to-treat analyses to preserve temporal alignment between treatment initiation and outcome assessment.

The emulated target trial sought to answer whether initiation of JAK inhibitors, compared with biologic therapies, was associated with differential risk of progression to psoriatic arthritis. In the hypothetical target trial, eligible participants would be randomized to initiate either a JAK inhibitor or a biologic comparator and followed longitudinally for incident PsA. In the observational emulation, treatment assignment was approximated using 1:1 propensity score matching between JAK inhibitor initiators and each biologic comparator group (IL-17 and IL-23 inhibitors). Matching was performed using a nearest-neighbor algorithm without replacement.

### Covariates for Propensity Score Matching

Propensity score models included baseline demographic, clinical, and medication-related covariates selected a priori based on clinical relevance and prior literature. These covariates included age at index date, sex, race and ethnicity, and comorbid conditions such as hypertension, hyperlipidemia, type 2 diabetes mellitus, overweight or obesity, atopic dermatitis, heart failure, gastroesophageal reflux disease, depressive disorders, anxiety disorders, joint pain, and dorsalgia. Baseline medication exposures included methotrexate use, other immunosuppressant use, and systemic corticosteroid use. Comorbidities were defined using ICD-10 codes, and medication exposures were defined using RxNorm and ATC classifications.

### Outcomes

The primary outcome was incident psoriatic arthritis, defined using the ICD-10 code L40.5. Patients with PsA diagnosed prior to the index date were excluded. Outcomes were assessed from 1 day after treatment initiation through a maximum follow-up of 5 years. To evaluate residual confounding and outcome specificity, several sensitivity and negative control outcomes were prespecified, including fracture of the lower end of the radius (S52.5), presbyopia (H52.4), nephrolithiasis (N20), and ingrown nail (L60.0). These outcomes were also assessed from 1 day through 5 years after index therapy initiation, with patients excluded if the outcome occurred prior to the index date.

**Follow-up**

Patients were followed from 1 day after the index date until the occurrence of the outcome of interest, loss to follow-up, death, or 5 years of follow-up, whichever occurred first. Analyses were conducted under an intention-to-treat framework, consistent with the target trial specification.

**Statistical Analysis**

Baseline characteristics were compared between matched cohorts to assess covariate balance. Time-to-event analyses were performed using Cox proportional hazards regression models to estimate hazard ratios and corresponding 95% confidence intervals (CIs) for incident psoriatic arthritis. Kaplan-Meier survival curves were generated, and differences between groups were assessed using log-rank tests. Risk analyses were conducted for both the primary outcome and sensitivity and negative control outcomes to assess robustness and potential residual confounding.

## RESULTS

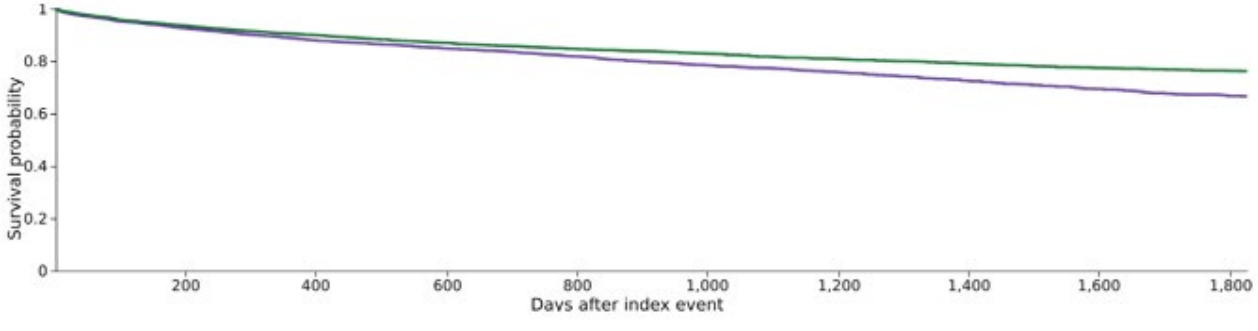
With those on IL-23 inhibitors (n=5,027 per group, mean follow up 888 vs 925 days), incident PsA occurred in 19.0% of JAK inhibitor users and 15.1% on IL-23 inhibitors, corresponding to a higher risk with JAK inhibitors (risk ratio [RR] 1.25, 95% CI 1.15-1.37; hazard ratio [HR] 1.32, 95% CI 1.20-1.46; log-rank *P*<0.0001).

Compared with IL-17 inhibitors (n=5,300 per group, mean follow up 850 vs 1017 days), incident PsA occurred in 16.8% of JAK inhibitor users compared with 27.1% on IL-17 inhibitors, indicating a significantly lower risk among JAK inhibitor initiators (RR 0.62, 95% CI 0.58-0.67; HR 0.66, 95% CI 0.61-0.72; log-rank *P*<0.0001). Kaplan-Meier analyses demonstrated consistent separation of PsA-free survival curves across both comparisons (Figures 1–2). Negative controls demonstrated no increased risk or hazard in both analyses (Tables 1–2).

## DISCUSSION

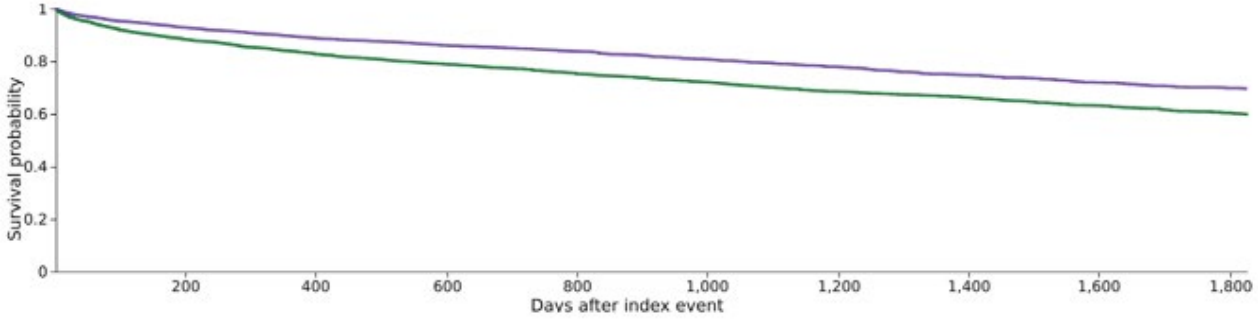
In this large, real-world, propensity score–matched analysis, IL-23 inhibitors were associated with the lowest observed incidence of incident PsA among patients with psoriasis, followed by JAK inhibitors and IL-17 inhibitors. Although IL-17 inhibitors are often associated with more rapid initial cutaneous clearance, accumulating evidence suggests that IL-23 inhibition confers more durable disease control, including sustained improvements in PASI scores and reductions in patient-reported pain over longer follow-up periods.[11,15] Our findings extend these observations by suggesting that IL-23-targeted therapies may also be associated with a lower subsequent risk of PsA, supporting the concept that upstream modulation of the Th17 axis may have implications beyond skin-limited disease.

**FIGURE 1.** Kaplan-Meier curve for PsA free survival for JAK Inhibitors vs IL-23 Inhibitors, assessed over 5 years.




Green curve= IL-23 Inhibitors, Purple curve= JAK inhibitors.

**FIGURE 2.** Kaplan-Meier curve for PsA free survival for JAK Inhibitors vs IL-17 Inhibitors, assessed over 5 years.




Green curve= IL-23 Inhibitors, Purple curve= JAK inhibitors.

**TABLE 1.**

**Composite Table Displaying Matched Baseline Characteristics (With Standardized Mean Differences)**

| Variable | Code | IL-23.JAK n (%)/Mean± SD | IL-23-Interleukin n (%)/Mean±SD | Std diff. | IL-17.JAK n (%)/ Mean±SD | IL-17-Interleukin n (%)/Mean ± SD | Std diff. |
|---|---|---|---|---|---|---|---|
| Age at index (years) | AI | 5,027 (51.1 ± 17.1) | 5,027 (51.1 ± 17.5) | D.D04 | 5,3D0(50.9± 17.1) | 5,3D0 (51.2 ± 16.4) | D.D17 |
| Male sex | M | 1,732 (34.5%) | 1,707 (34.0%) | 0.007 | 1,855 (35.0%) | 1,804 (34.0%) | 0.015 |
| White | 2106-3 | 3,843 (76.4%) | 3,829 (76.2%) | -<0.001 | 4,009 (75.6%) | 4,042 (76.3%) | 0.011 |
| Black or African American | 2054-5 | 359 (7.1%) | 380 (7.6%) | 0.016 | 419 (7.9%) | 425 (8.0%) | 0.004 |
| Hispanic or Latino | 2135-2 | 326 (6.5%) | 326 (6.5%) | 0.01 | 341 (6.4%) | 327 (6.2%) | 0.02 |
| Asian | 2028-9 | 268 (5.3%) | 252 (5.0%) | 0.014 | 285 (5.4%) | 258 (4.9%) | 0.023 |
| Hypertensive disease | 110-115 | 1,678 (33.4%) | 1,709 (34.0%) | D.013 | 1,674 (31.6%) | 1,664 (31.4%) | 0.004 |
| Hyperlipidemia | E78.5 | 1,104 (22.0%) | 1,117 (22.2%) | D.006 | 1,101 (20.8%) | 1,128 (21.3%) | 0.013 |
| Type 2 diabetes mellitus | E11 | 712 (14.2%) | 692 (13.8%) | 0.058 | 748 (14.1%) | 733 (13.8%) | 0.012 |
| Ove rweightlobesity | E66 | 1,092 (21.7%) | 1,093(21.7%) | D.004 | 1,133 (21.4%) | 1,099 (20.7%) | 0.024 |
| Nicotine dependence | F17.21 | 361 (7.2%) | 374 (7.4%) | -<0.001 | 365 (6.9%) | 361 (6.8%) | 0.016 |
| Alcohol-related disorders | F10 | 145 (2.9%) | 148 (2.9%) | 0.011 | 151 (2.8%) | 173 (3.3%) | 0.008 |
| Heart failure | 150 | 252 (5.0%) | 276 (5.5%) | 0.01 | 241 (4.5%) | 236 (4.5%) | 0.003 |
| GERO | K21 | 1,166 (23.2%) | 1,203 (23.9%) | D.024 | 1,136(21.4%) | 1,128 (21.3%) | 0.0D7 |
| Noninfective enteritis/colitis | K50-K52 | 654 (13.0%) | 755 (15.0%) | 0.021 | 584 (11.0%) | 565 (10.7%) | 0.005 |
| Atopic dermatitis | L2D | 541 (10.8%) | 579 (11.5%) | D.017 | 455 (8.6%) | 444 (8.4%) | 0.004 |
| Psoriasis, unspecified | L4D.9 | 2,027 (40.3%) | 2,002 (39.8%) | D.023 | 2,252 (42.5%) | 2,193 (41.4%) | 0.014 |
| Generalized pustular psoriasis | L4D.1 | 359 (7.1%) | 389 (7.7%) | D.019 | 422 (8.0%) | 443 (8.4%) | 0.012 |
| Palmoplantar pustulosis | L4D.3 | 437 (8.7%) | 464 (9.2%) | D.016 | 508 (9.6%) | 527 (9.9%) | 0.0D1 |
| Guttate psoriasis | L40.4 | 376 (7.5%) | 397 (7.9%) | 0.01 | 447 (8.4%) | 449 (8.5%) | 0.023 |
| Depressive episode | F32 | 895 (17.8%) | 904 (18.0%) | D.005 | 911 (17.2%) | 894 (16.9%) | 0.0D9 |
| Anxiety disorders | F41 | 1,159 (23.1%) | 1,176 (23.4%) | D.008 | 1,152(21.7%) | 1,139 (21.5%) | 0.0D6 |
| Joint pain | M25.5 | 1,853 (36.9%) | 1,885 (37.5%) | 0.013 | 1,840 (34.7%) | 1,806 (34.1%) | 0.014 |
| Dorsalgia | M54 | 1,541 (30.7%) | 1,520 (30.2%) | 0.009 | 1,539 (29.0%) | 1,515 (28.6%) | 0.01 |
| Enthesopathies | M77 | 289 (5.7%) | 297 (5.9%) | D.007 | 285 (5.4%) | 273 (5.2%) | 0.01 |
| Digestive organ malignancy | C15-C26 | 34 (0.7%) | 39 (0.8%) | D.012 | 28 (0.5%) | 30 (0.6%) | 0.0D5 |
| Respiratory malignancy | C30-C39 | 17(0.3%) | 17 (0.3%) | -<0.001 | 18(0.3%) | 20 (0.4%) | 0.0D6 |
| Breast cancer | C50 | 64(1.3%) | 62 (1.2%) | D.004 | 71 (1.3%) | 72 (1.4%) | 0.0D2 |
| Male genital malignancy | C60-C63 | 51 (1.0%) | 50 (1.0%) | D.002 | 49 (0.9%) | 46 (0.9%) | 0.0D6 |
| Urinary tract malignancy | C64-C68 | 28 (0.6%) | 28 (0.6%) | -<0.001 | 26 (0.5%) | 23 (0.4%) | 0.008 |
| Hematologic malignancy | C81-C96 | 133 (2.6%) | 136 (2.7%) | 0.004 | 116 (2.2%) | 104 (2.0%) | 0.016 |
| Phototherapy | 6A6 | 10(0.2%) | 10 (0.2%) | -<0.001 | 0 (0.0%) | 10 (0.2%) | 0.061 |
| Immunosuppressants (any) | L04 | 2,643 (52.6%) | 2,634 (52.4%) | D.004 | 2,823 (53.3%) | 2,801 (52.8%) | 0.0D8 |
| Systemic corticosteroids | H02 | 3,714 (73.9%) | 3,733 (74.3%) | 0.009 | 3,818 (72.0%) | 3,857 (72.8%) | 0.016 |
| Methotrexate | 6851 | 996 (19.8%) | 949 (18.9%) | D.024 | 1,02D(19.2%) | 1,008 (19.0%) | 0.0D6 |
| Cyclosporine | 30D8 | 198 (3.9%) | 215 (4.3%) | D.017 | 227 (4.3%) | 203 (3.8%) | 0.023 |
| Acitretin | 16818 | 73(1.5%) | 78 (1.6%) | 0.008 | 79(1.5%) | 82 (1.5%) | 0.005 |
| Sulfasalazine | 9524 | 159 (3.2%) | 158 (3.1%) | D.001 | 193 (3.6%) | 201 (3.8%) | 0.0D8 |
| ESR measured | 9066 | 1,590 (31.6%) | 1,581 (31.5%) | D.052 | 1,566 (29.5%) | 1,576 (29.7%) | 0.018 |
| ESR 0-20 mm/h | -- | 1,107 (22.0%) | 1,117 (22.2%) | 0.005 | 1,084 (20.5%) | 1,079 (20.4%) | 0.002 |
| ESR >20 mm/h | -- | 878 (17.5%) | 906 (18.0%) | 0.015 | 842 (15.9%) | 841 (15.9%) | 0.001 |
| Ambulatory visit | AMB | 4,240 (84.3%) | 4,214 (83.8%) | D.014 | 4,477 (84.5%) | 4,479 (84.5%) | 0.0D1 |
| Emergencv visit | EMER | 1,451 (28.9%) | 1,455 (28.9%) | 0.002 | 1,432 (27.0%) | 1,412 (26.6%) | 0.009 |
| Inpatient encounter | IMP | 1,158 (23.0%) | 1,200 (23.9%) | D.02 | 1,136(21.4%) | 1,116 (21.1%) | 0.0D9 |

**TABLE 2.**

**Composite Table Displaying Post-Matching Outcome Analyses, Including Risk Estimates, Risk Ratios, Hazard Ratios, and Log-Rank Statistics For JAK Inhibitors vs Interleukin Inhibitors.**

| | Variable/Outcome | Code | JAK Group n (%) or Mean ± SD | Comparator Group n (%) or Mean ± SD | Risk/RR (95% CI) | HR (95% CI) | Log-rank *P* |
|---|---|---|---|---|---|---|---|
| IL-23 | Psoriatic arthritis | ICD-10 L40.5 | 953/5,027 (19.0%) | 761/5,027 (15.1%) | 1.25 (1.15-1.37) | 1.32 (1.20-1.46) | <0.0001 |
| | Fracture (negative control) | ICD-10 S52.5 | 15/4,968 (0.3%) | 19/4,969 (0.4%) | 0.79 (0.40-1.55) | 0.82 (0.42-1.62) | 0.567 |
| | Presbyopia (negative control) | ICD-10 H52.4 | 78/4,816 (1.6%) | 79/4,831 (1.6%) | 0.99 (0.73-1.35) | 1.03 (0.76-1.41) | 0.841 |
| | Nephrolithiasis (negative control) | ICD-10 N20 | 127/4,740 (2.7%) | 114/4,730 (2.4%) | 1.11 (0.87-1.43) | 1.16 (0.90-1.50) | 0.246 |
| | Ingrown nail (negative control) | ICD-10 L60.0 | 52/4,940 (1.1%) | 37/4,935 (0.7%) | 1.40 (0.92-2.14) | 1.46 (0.96-2.23) | 0.075 |
| IL-17 | Psoriatic arthritis | ICD-10 L40.5 | 890/5,304 (16.8%) | 1,434/5,304 (27.1%) | 0.62 (0.58-0.67) | 0.66 (0.61-0.72) | <0.0001 |
| | Fracture (negative control) | ICD-10 S52.5 | 16/5,248 (0.3%) | 25/5,246 (0.5%) | 0.64 (0.34-1.20) | 0.77 (0.41-1.44) | 0.413 |
| | Presbyopia (negative control) | ICD-10 H52.4 | 84/5,088 (1.6%) | 87/5,101 (1.7%) | 0.97 (0.72-1.31) | 1.15 (0.85-1.56) | 0.350 |
| | Nephrolithiasis (negative control) | ICD-10 N20 | 120/5,030 (2.4%) | 121/5,028 (2.4%) | 0.99 (0.78-1.28) | 1.17 (0.91-1.51) | 0.214 |
| | Ingrown nail (negative control) | ICD-10 L60.0 | 44/5,210 (0.8%) | 46/5,206 (0.9%) | 0.96 (0.63-1.44) | 1.13 (0.75-1.72) | 0.551 |

From a mechanistic standpoint, IL-23 occupies a central position in the differentiation and maintenance of pathogenic Th17 cells and may play a more direct role in driving chronic entheseal and synovial inflammation than IL-17 alone.[16] Persistent IL-23 signaling has been implicated in the transition from cutaneous inflammation to musculoskeletal disease, raising the possibility that earlier or sustained IL-23 blockade may attenuate pathways involved in PsA pathogenesis. While JAK inhibitors act downstream by broadly suppressing multiple cytokine signals, their comparatively less targeted immunomodulatory profile may account for the intermediate associations observed in this study. These biologic considerations provide plausibility for the observed class-specific differences, although they do not establish causality.

Several important limitations merit careful consideration. First, PsA diagnosis was ascertained using ICD-10 codes, introducing potential misclassification and limiting the ability to evaluate clinical phenotype, disease severity, or subclinical musculoskeletal involvement. Similarly, psoriasis severity, disease duration, nail involvement, and family history, well-established predictors of PsA, were not directly measurable within TriNetX and may contribute to residual confounding despite extensive matching.[17-19] However, we partially mitigated this limitation by adjusting for baseline musculoskeletal symptoms, healthcare utilization, comorbidities, prior systemic therapies, and psoriasis subtypes, which serve as clinically relevant proxies for disease burden.

Second, channeling bias is an important consideration, with these agents frequently prescribed in patients with prominent joint symptoms or refractory disease.[20] This prescribing pattern may have enriched the JAK inhibitor cohort with individuals already at elevated baseline risk for PsA, potentially biasing estimates toward higher observed incidence. Notably, despite this bias, JAK inhibitors demonstrated a lower incidence of PsA compared with IL-17 inhibitors, underscoring the robustness of the observed associations. Importantly, relative comparisons rather than absolute incidence rates are the primary focus of this analysis, especially given follow-up duration, and outcome ascertainment.

Despite these limitations, this study has several notable strengths that enhance its relevance. We employed a TARGET trial emulation framework with active comparators and rigorous propensity score matching, reducing immortal time bias and confounding by indication. The large, multisite nature of the dataset increases generalizability to routine clinical practice, capturing prescribing patterns and outcomes that may not be observable in randomized trials. Furthermore, our study addresses a critical evidence gap, as head-to-head randomized trials evaluating PsA prevention across biologic and small-molecule classes are unlikely to be conducted. Taken together, these findings should be viewed as hypothesis-generating but clinically informative. In the absence of prospective prevention trials, real-world comparative effectiveness studies such as this provide valuable insights into how therapeutic choices may influence long-term disease trajectories.

## CONCLUSION

In this large real-world cohort of patients with psoriasis, IL-23 inhibitors were associated with the lowest observed incidence of PsA, followed by JAK inhibitors and IL-17 inhibitors. Although causal inference cannot be established, these results suggest that upstream targeting of the IL-23/Th17 axis may have implications for PsA risk and may inform therapeutic decision-making in patients with psoriasis who are at elevated risk for musculoskeletal disease. Future studies incorporating longitudinal clinical assessments, imaging, and biomarker data are needed to further elucidate mechanisms and validate these associations.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

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

## REFERENCES

1. Strober B, Soliman AM, Li C, et al. Risk of developing inflammatory arthritis in patients with psoriasis initiating treatment with biologics: a population-based analysis. *J Am Acad Dermatol.* 2024;91(6):1143-1149. doi:10.1016/j.jaad.2024.06.106
2. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. *Autoimmun Rev.* 2017;16(1):10-15. doi:10.1016/j.autrev.2016.09.015. PMID: 27666819.
3. Gisondi P, Bellinato F, Galeone C, et al. Risk of developing psoriatic arthritis in patients with psoriasis initiating treatment with different classes of biologics. *Ann Rheum Dis.* 2025;84(3):435-441. doi:10.1016/j.ard.2025.01.006. PMID: 39919973.
4. Acosta Felquer ML, LoGiudice L, Galimberti ML, et al. Treating the skin with biologics in patients with psoriasis decreases the incidence of psoriatic arthritis. *Ann Rheum Dis.* 2022;81(1):74-79. doi:10.1136/annrheumdis-2021-220865. PMID: 34281904.
5. Floris A, Mugheddu C, Sichi L, et al. Treatment of psoriasis with different classes of biologics reduces the likelihood of peripheral and axial psoriatic arthritis development. *Rheumatology (Oxford).* 2025;64(3):1131-1137. doi:10.1093/rheumatology/keae257. PMID: 38781521.
6. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet.* 2007;370(9583):263-271. doi:10.1016/S0140-6736(07)61128-3. PMID: 17658397.
7. Tonel G, Conrad C, Laggner U, et al. Cutting edge: a critical functional role for IL-23 in psoriasis. *J Immunol.* 2010;185(10):5688-5691. doi:10.4049/jimmunol.1001538. PMID: 20956338.
8. Ghoreschi K, Balato A, Enerbäck C, et al. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet.* 2021;397(10275):754-766. doi:10.1016/S0140-6736(21)00184-7. PMID: 33515492.
9. Fragoulis GE, Siebert S. The role of IL-23 and the use of IL-23 inhibitors in psoriatic arthritis. *Musculoskeletal Care.* 2022;20 Suppl 1(Suppl 1):S12-S21. doi:10.1002/msc.1694. PMID: 36069174.
10. Dilek G, Kalcik Unan M, Nas K. Immune response and cytokine pathways in psoriatic arthritis: a systematic review. *Arch Rheumatol.* 2025;40(1):144-156. doi:10.46497/ArchRheumatol.2025.10934. PMID: 40264485.
11. Agüero R, Woodbury MJ, Lee K, et al. Interleukin (IL)-17 versus IL-23 inhibitors: which is better to treat patients with moderate-to-severe psoriasis and mild psoriatic arthritis in dermatology clinics?. *J Rheumatol.* 2023;50(Suppl 2):11-13. doi:10.3899/jrheum.2023-0511
12. Raychaudhuri S, Jayeshbhai Shah R, Raychaudhuri SK, et al. Janus kinase inhibitors for the treatment of psoriatic arthritis. *Indian J Dermatol Venereol Leprol.* 2023:1-6. doi:10.25259/IJDVL_29_2023. PMID: 37609752.
13. Barsoum M, Mohamed M, Ibrahim A, et al. Janus kinase inhibitors as emerging therapy in the treatment of psoriatic arthritis: a narrative review of efficacy, safety, and future perspective. *Cureus.* 2025;17(9):e92166. doi:10.7759/cureus.92166. PMID: 40949078.
14. Yu S, Huo AP, Wang YH, et al. Interleukin-23 versus interleukin-17 inhibitors in preventing incidental psoriatic arthritis in patients with psoriasis: a real-world comparison from the TriNetX US collaborative network. *BioDrugs.* 2025;39(2):297-306. doi:10.1007/s40259-025-00705-5
15. Dattola A, Bernardini N, Anedda J, et al. Real-world analysis of IL-23 inhibitors in patients with moderate-to-severe psoriasis and early musculoskeletal symptoms. *Drugs Context.* 2025;14:2025-5-1. doi:10.7573/dic.2025-5-1. PMID: 40948988.
16. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417. doi:10.1016/j.jaad.2016.11.041. PMID: 28057360.
17. Zabotti A, De Lucia O, Sakellariou G, et al. Predictors, risk factors, and incidence rates of psoriatic arthritis development in psoriasis patients: a systematic literature review and meta-analysis. *Rheumatol Ther.* 2021;8:1519-1534. doi:10.1007/s40744-021-00378-w
18. Papoutsaki M, Costanzo A. Treatment of psoriasis and psoriatic arthritis. *BioDrugs.* 2013;27 Suppl 1:3-12. doi:10.1007/BF03325637. PMID: 23990277.
19. Fratton Z, Giovannini I, Zabotti A, et al. Skin and nail predictors of psoriatic arthritis development: a holistic overview integrating epidemiological and physiopathological data. *J Clin Med.* 2024;13(22):6880. doi:10.3390/jcm13226880. PMID: 39598023.
20. Gialouri CG, Evangelatos G, Fragoulis GE. Choosing the appropriate target for the treatment of psoriatic arthritis: TNFα, IL-17, IL-23 or JAK inhibitors?. *Mediterr J Rheumatol.* 2022;33(Suppl1):150-161. doi:10.31138/mjr.33.1.150

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Impetigo Antibiotic Stewardship and the Need for Treatment Alternatives

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## ABSTRACT

**Background:** Impetigo is a highly contagious bacterial skin infection, primarily caused by *Staphylococcus aureus* and, less frequently, *Streptococcus pyogenes*. Although typically self-limiting, treatment is recommended to reduce symptom burden, limit transmission, and prevent complications. Increasing antimicrobial resistance to commonly used topical antibiotics presents a growing challenge, highlighting the need to develop new topical antibiotics and incorporate antibiotic stewardship principles into impetigo management.

**Methods:** A structured literature review was conducted to evaluate the clinical efficacy, safety, and antimicrobial resistance associated with topical treatments for impetigo. An international panel of dermatologists, including pediatric dermatologists and a pediatrician, convened in February 2026 to review the evidence and provide clinical insights on stewardship-informed management strategies.

**Results:** Topical antibiotics remain first-line therapy for localized uncomplicated impetigo. However, resistance to topical antibiotics commonly used to treat impetigo (eg, mupirocin, fusidic acid, and retapamulin) has been widely reported. Antibiotic stewardship is an essential component of impetigo management and promotes the use of the right antibiotic for the right duration. Topical ozenoxacin, which acts against organisms resistant to other topical agents and has a low capacity for developing resistance, may help address existing gaps and support stewardship-informed care.

**Conclusions:** Impetigo represents an important opportunity for antimicrobial stewardship in dermatology. Consideration of local trends in antibiotic resistance, antibiotic-sparing strategies, and use of novel agents may help optimize management and address current limitations in care.

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## INTRODUCTION

Increasing rates of antimicrobial resistance in clinical practice underscore the importance of antibiotic stewardship in improving patient outcomes.[1] While stewardship efforts have largely focused on systemic infections, superficial skin infections such as impetigo represent an important opportunity to optimize antibiotic prescribing.

Impetigo is 1 of the most common bacterial skin infections, with over 3 million cases reported in the United States every year.[1,2] Although most common in children aged 2 to 5 years, impetigo can occur across all age groups.[3] Impetigo is primarily caused by *Staphylococcus aureus* (*S. aureus*) and less frequently by both *S. aureus* and *Streptococcus pyogenes* (*S. pyogenes*) or just *S. pyogenes*. Both *S. aureus* and *S. pyogenes* cause the

nonbullous form of impetigo, which occurs in approximately 70% of cases.[1,3] This type of impetigo begins as erythematous papules, usually smaller than 2 cm, that rapidly evolve into vesicles and pustules that rupture, with the dried discharge forming honey-colored crusts on an erythematous base.[4] Lesions primarily occur on the face around the nose and mouth, but can also present elsewhere on the body.[3]

In contrast, bullous impetigo, which is caused exclusively by *S. aureus*, results in large, fragile, thin-roofed vesicopustules that may rupture, creating crusted, erythematous erosions, often surrounded by a collar of the roof's remnants.[1,4] They occur primarily in intertriginous areas and the trunk.[3] The risk of complications requiring hospital admission is higher for bullous than nonbullous impetigo.[3]

Although impetigo is often regarded as a self-limiting disease, treatment is important for symptom control, limiting the spread of infection, and reducing the risk of complications.[5] However, increasing rates of antibiotic resistance to commonly prescribed topical agents pose a challenge in impetigo management.

Despite growing recognition of antimicrobial resistance, there remains limited guidance on applying antibiotic stewardship principles specifically to the management of impetigo. In particular, there is a lack of attention to antibiotic resistance in impetigo, as well as limited information on resistance to topical antibiotic agents used to treat it. This review aims to address these gaps by examining the role of antibiotic stewardship in impetigo and providing clear guidance that clinicians can take to their practices.

## MATERIALS AND METHODS

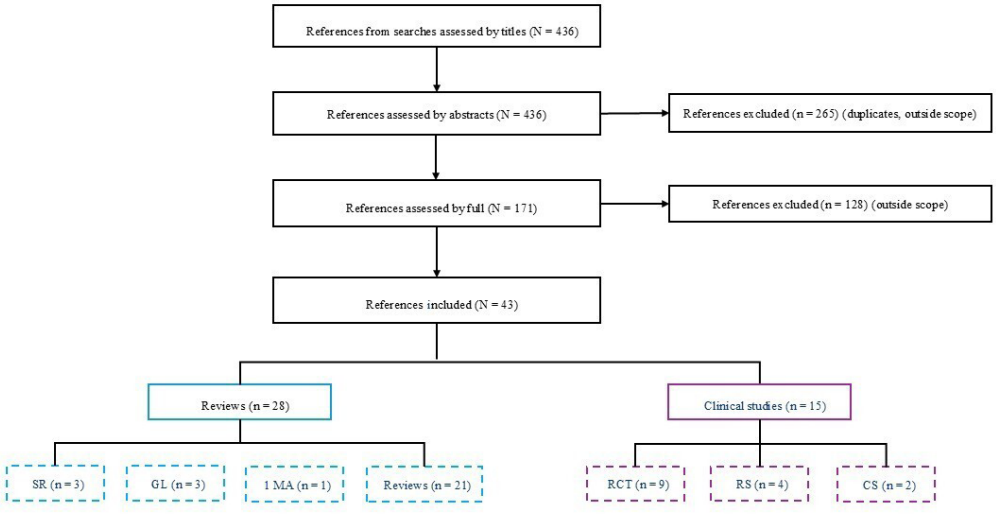
### Scope and Preliminary Considerations

This manuscript provides clinical insights into the management of impetigo in the context of antibiotic stewardship. It was developed using a structured process that included a literature review and expert panel discussion. Following the literature search, an international panel of 9 dermatologists, pediatric dermatologists, and a pediatrician met on February 4, 2026, in Miami, FL to discuss the results of the literature review on stewardship-focused impetigo management.

### Literature Review

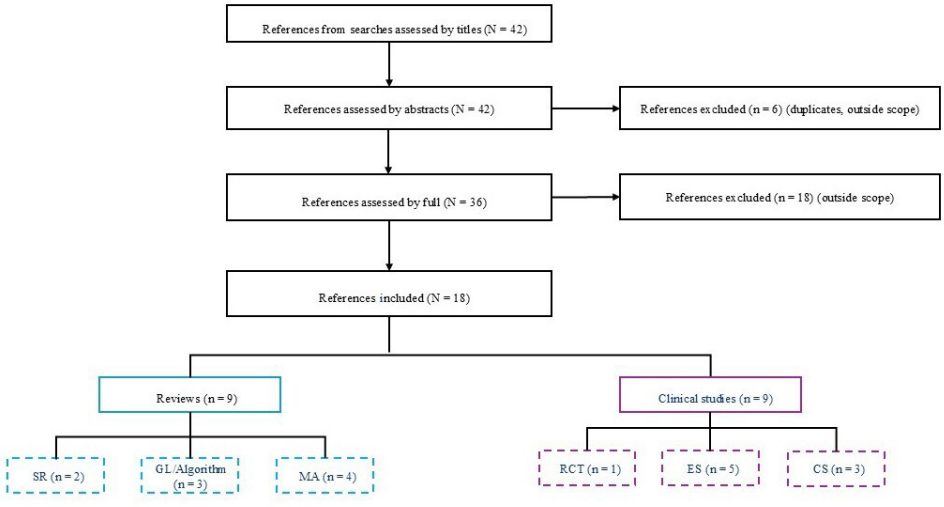
A systematic literature search was conducted prior to the meeting to inform the development of a manuscript on stewardship-informed treatment of impetigo. The systematic review included research studies, clinical guidelines, consensus papers, and English-language reviews published from 2014 to 2020 that addressed aspects of impetigo management, including the clinical efficacy and safety of treatment, antimicrobial resistance, costs, quality-of-life effects, and treatment regimen tolerability. These searches were then updated with a structured review using the same methodology to include articles from January 2021 to November 2025. For the literature search, the following terms were used: *impetigo; bullous impetigo; non-bullous impetigo; impetigo pathogenesis and diagnosis; topical and systemic impetigo treatment; adjunctive impetigo treatment; adherence; concordance; efficacy; safety; tolerability; antimicrobial and antibiotic resistance.*

**FIGURE 1A.** Systematic literature review results.




Adapted with permission from Schachner LA et al. *J Drugs Dermatol.* 2021;20(2):134-142. doi:10.36849/JDD.5745[3]
The systematic review included research studies, clinical guidelines, consensus papers, and English-language reviews published from 2014 to 2020 that addressed aspects of impetigo management, including the clinical efficacy and safety of treatment, antimicrobial resistance, costs, quality-of-life effects, and treatment regimen tolerability.
Out of scope: Study with a small number, case studies, in-vitro or in-vivo studies, animal studies.
Clinical studies (CS); Randomized controlled trials (RCT); Retrospective studies (RS); Cross-sectional studies (CS); Systematic reviews (SR); Guidelines (GL); Meta-analysis (MA).

**FIGURE 1B.** Updated literature review results.




The systematic literature searches were updated with a structured review using the same methodology to include articles from January 2021 through November 2025.
Out of scope: Studies with a small number, case studies, in vitro or in vivo studies, animal studies.
Clinical studies (CS); Randomized controlled trials (RCT); Retrospective studies (RS); Cross-sectional studies (CS); Systematic reviews (SR); Guidelines (GL); Meta-analysis (MA); Epidemiology studies (ES).

Titles and abstracts were reviewed first, followed by the full articles. Publications were excluded if they had a small number of participants, or were case studies, animal studies, or published in a language other than English. The initial search yielded 436 results (including duplicates); after review, 43 articles were deemed relevant to a manuscript on antibiotic use and stewardship in impetigo (Figure 1A). The systematic literature searches were updated with a structured review using the same methodology to include references from January 2021 to November 2025. The initial search yielded 42 references, and after abstract and full-text review 18 references were included (Figure 1B).

Following the literature review, the panel of advisors participated in a face-to-face meeting to discuss stewardship-focused impetigo management and to develop a manuscript on impetigo treatment in the context of antimicrobial stewardship.

## RESULTS

### Impetigo Management Principles

Impetigo is a highly contagious bacterial infection that affects the superficial layers of the skin.[6] Transmission in children occurs through contact with infected individuals or pets, fomites, particularly in schools, daycare centers, and crowded housing, while sources for adults include infected children and self-inoculation from nasal or perineal carriage.[3] Impetigo is more common in warm, humid climates, conditions of poor hygiene (eg, overcrowding), and in people with underlying skin conditions (eg, scabies).[3]

Most cases of impetigo resolve within 2 to 3 weeks without scarring.[3] Although complications are uncommon, particularly in non-bullous impetigo, local and systemic spread may occur, resulting in cellulitis, lymphangitis, or, rarely, septicemia. Infections caused by *Streptococcus pyogenes* may also lead to complications such as guttate psoriasis or poststreptococcal glomerulonephritis.[3] Therefore, treatment is pursued to prevent the spread of infection, reduce the risk of complications, hasten symptom resolution, and minimize scarring due to scratching.[1,3]

Management of impetigo includes both nonpharmacologic and pharmacologic strategies. Gentle cleansing and crust removal are an important part of treatment.[2,7] To limit the spread of infection, children are also recommended to be kept at home until 24 h after the start of appropriate antimicrobial therapy.[1]

Both bullous and nonbullous impetigo may be managed with either topical or oral antibiotics, depending on disease severity and distribution.[3] Current guidelines recommend topical antibiotics as first-line therapy for patients with limited disease, while oral antibiotics are reserved for more extensive involvement.[4-7] Impetiginized eczema is also treated with either oral or topical antibiotics, depending on the size of the affected area(s) and number of infection sites.[8]

Topical treatment for impetigo includes fusidic acid (not available in the United States, but used in other countries including Canada, UK, and Australia), mupirocin, retapamulin (no longer available), and more recently, ozenoxacin 1% cream

(Table 1).[2-4,6-10] These agents deliver a high concentration of drug to infected skin with low systemic absorption and lower risk of adverse effects (AEs) than oral antibiotics, supporting their use as first-line therapy in localized mild-to-moderate impetigo.[1,2] Prior to the introduction of ozenoxacin, there were limited therapeutic advances in the treatment of impetigo for several years.

Accordingly, much of the efficacy evidence in impetigo for topical antibiotics comes from older studies, but the applicability of these outcomes to present-day practice may be limited by evolving antibiotic use and resistance patterns. A Cochrane review found that topical fusidic acid and mupirocin are as effective as, or more effective than, oral treatment for limited impetigo, supporting their role as first-line therapy for localized disease.[11] Topical mupirocin was also found to be superior to the oral antibiotic, oral erythromycin.[11] However, direct comparative studies between individual topical agents are limited, and differences in study design, patient populations, local resistance patterns, and outcome measures make it difficult to establish clear superiority among available treatments. Furthermore, a meta-research analysis evaluating the methodological quality of randomized controlled trials (RCTs) on pharmacologic treatments for impetigo identified several concerns, including unclear randomization and allocation concealment procedures, high risk of bias related to blinding, and high risk of attrition bias. These findings highlight the need for more rigorous trial design and reporting standards to strengthen the reliability of evidence guiding impetigo management.[12]

**Antibiotic Resistance in Impetigo**

An increasing number of Gram-positive pathogens, especially *S. aureus*, have developed resistance to topical antimicrobial agents commonly used in clinical practice.[1] Indeed, antimicrobial resistance (AMR) has emerged as a major global health concern, with the World Health Organization (WHO) identifying it as 1 of the top threats to public health.[13] AMR not only makes infections harder to treat, but also creates the need for more expensive and intensive care.[13,14] In the context of impetigo, resistance has been reported to many of the most frequently prescribed topical treatments, including mupirocin, fusidic acid, and retapamulin

**TABLE 1.**

**Topical Antimicrobials for Impetigo**

| Name of Drug | FDA Approval Date | Indication | Dosing Regimen | Mechanism of Action | Antimicrobial activity |
|---|---|---|---|---|---|
| Fusidic Acid | N/A in the United States; approved in other countries (UK, Canada, Australia) | No age limitation stated in the PI | TID x 7-10 days | Inhibits protein synthesis through locking EF-G to the ribosome | Active against *S. aureus, Streptococcus spp.* and *Corynebacterium minutissimum* |
| Mupirocin | 2003 | Impetigo in patients >2 months old | TID x 7-10 days | Reversibly inhibits bacterial protein and RNA synthesis by isoleucyl-tRNA synthetase | Effective against gram-positive bacteria, especially *S. aureus* including MRSA and *Streptococci* |
| Ozenoxacin | 2017 | Impetigo in patients >2 months old* | BID x 5 days | Dual inhibitor of DNA replication enzymes, blocks DNA gyrase and topoisomerase IV | Effective against gram-positive bacteria (*S. aureus*, MRSA, *S. pyogenes*)<br>Efficacy against mupirocin-resistant *S. aureus*, fusidic acid resistant *S. aureus*, quinolone-resistant *S. aureus*, and clinda-mycin-resistant *S. aureus* |
| Retapamulin† | 2007 | Impetigo in patients >9 months old | BID x 5 days | Inhibition of protein synthesis by interacting with the 50S subunit of bacterial ribosomes at protein L3 and subsequent prevention of active 50S subunit formation | Active against *S. aureus* (methicillin susceptible isolates only) and *S. pyogenes* |

BID, twice daily; EF-G, elongation factor G; MRSA, methicillin-resistant Staphylococcus aureus; TID, 3 times daily.
*In EU countries, 6 months of age and older.
†Retapamulin is no longer available

**TABLE 2.**

**Global Prevalence and Mechanisms of *S. aureus* Resistance to Topical Antibiotics for Impetigo**

| Name of Drug | *S. aureus* Resistance (%)* | Mechanism of *S. aureus* Resistance |
|---|---|---|
| Fusidic Acid | 5.9%–51.9% | In *S. aureus*, there are three mechanisms of resistance:<br>a. Mutations in the antibiotic target, EF-G<br>b. Expression of resistance proteins that provide target protection<br>c. Mutations in a ribosomal protein, uL6 (uncommon) |
| Mupirocin | 1.1%–37.7% | *S. aureus* resistance to mupirocin is often caused by acquisition of a novel isoleucyl-tRNA synthetase encoded on the plasmid gene *mup*A. |
| Ozenoxacin | No published clinical resistance signal/ data identified since introduction | Because ozenoxacin inhibits both DNA gyrase and topoisomerase IV equally, bacteria must develop multiple mutations in different enzymes simultaneously to become fully resistant. |
| Retapamulin† | 5%–14% | Resistance occurs through mutations in the genes encoding 23S rRNA but is not crossed with other antibiotics as the binding site is unique compared with those of other antibiotics acting on ribosomes. |

EF-G, elongation factor G; rRNA, ribosomal ribonucleic acid; *S. aureus, Staphylococcus aureus*; tRNA, transfer ribonucleic acid.
*Reported range across studies and geographies
†Retapamulin is no longer available

(Table 2).[3,6,10,15,16] While resistance patterns vary by region, evidence suggests that increased resistance to topical agents that are commonly used to treat impetigo may contribute to treatment failure and recurrent infection.[6]

The growing prevalence of AMR is particularly concerning in empirically managed diseases such as impetigo, where treatment is often initiated without microbiological confirmation or susceptibility testing.[1] As a result, local resistance patterns must be considered and should periodically be checked when making treatment decisions for patients with impetigo, as they can guide the choice of agent and avoid unnecessary antibiotic use.[2,3,7,14,17] In this context, the use of newer antimicrobial agents with different modes of action and with activity against resistant isolates may be appropriate.[1,18]

**Antibiotic Stewardship-Informed Treatment Principles**

Antimicrobial stewardship, defined by WHO as a systematic approach to educating and supporting health care professionals in following evidence-based guidelines for prescribing and administering antimicrobials, is critical to optimizing antibiotic use while preventing the development of resistance.[2,13] Incorporating antibiotic stewardship principles into the management of impetigo is essential, as dermatologists are among the most frequent prescribers of topical antibiotics.[2]

Stewardship-informed treatment for impetigo requires not only selecting therapy based on disease severity and extent but also considering local antibiotic resistance trends when choosing among available agents.[3] The panel noted that antibiotic stewardship does not imply avoidance of antibiotics, but rather the use of "the right antibiotic for the right amount of time." Minimizing unnecessary antibiotic exposure and avoiding overuse of antibiotics with known or increasing resistance are key components of this approach.

In intensive care units, antibiotic rotation has also been proposed to reduce antibiotic resistance by systematically rotating antibiotics or antibiotic classes for empirical treatment.[19] In recurrent impetigo, a topical antibiotic rotation regimen can be considered. An expert panel noted that the topical regimen may comprise a rotation of mupirocin and ozenoxacin cream 1% in the USA, while in Europe, a rotation of mupirocin, ozenoxacin, and fusidic acid may be used.[3]

Concerns regarding increased antimicrobial resistance have also prompted interest in nonantibiotic treatment options for impetigo. For example, the Treatment of Impetigo With Antiseptics – Replacing Antibiotics (TIARA) trial in New Zealand is designed to evaluate clinical improvement in childhood impetigo by comparing topical fusidic acid with topical hydrogen peroxide and simple wound care.[20]

Novel topical antibiotics may offer an additional treatment option for localized impetigo. Ozenoxacin cream is a non-fluorinated quinolone antibiotic approved in 2017 for the treatment of impetigo in patients aged 2 months and older. It acts by binding to DNA gyrase and topoisomerase IV, preventing bacterial replication and resulting in immediate cell death in bacterial pathogens.[6] Ozenoxacin has demonstrated potent bacteriostatic and bactericidal activity against Gram-positive bacteria, including both susceptible and resistant strains of *S. aureus* and *S. pyogenes*, including MRSA isolates.[3,21] Unlike other topical antibiotics, ozenoxacin has a low capacity for developing resistance, supported by its pharmacologic activity, which includes a low mutant selection rate, bactericidal effect at a low MIC, high in vitro antibacterial activity, and dermal concentrations above the mutant prevention concentration.[6]

**Ozenoxacin Cream 1%: Efficacy and Safety Data**

The efficacy and safety of ozenoxacin 1% cream in the treatment of impetigo have been demonstrated in 2 pivotal, placebo-controlled, phase 3 clinical trials.[21,22]

In the first randomized, double-blind, multicenter study, patients aged >2 years with impetigo received ozenoxacin 1% cream, placebo cream, or retapamulin 1% ointment twice daily for 5 days. The primary efficacy endpoint was clinical response (success or failure) in the intention-to-treat (ITT) clinical population at the end of therapy (visit 3; day 6–7). Clinical, microbiological, and laboratory evaluations were performed over a 2-week follow-up.[22] Analysis of the primary efficacy endpoint demonstrated that ozenoxacin was superior to placebo (success rate 34.8% vs 19.2%; *P*=0.003). Furthermore, ozenoxacin produced earlier clinical response and bacteriological eradication compared to the placebo group and more rapid microbiological clearance than retapamulin (success rate 74.7% vs 60.0% after 3–4 days; *P*=0.0087). All 3 treatment arms were well-tolerated, with a low incidence of treatment-emergent adverse events and no serious adverse events (AEs) or discontinuations due to AEs.[22]

The second randomized, double-blind, phase 3 clinical trial compared topical ozenoxacin 1% cream (n = 206) with placebo cream (n = 206) in patients aged 2 months or older with impetigo. The primary efficacy endpoint of the study was clinical response (clinical success or clinical failure) at the end of therapy in the ITT clinical population. Clinical success was defined as total absence of the treated lesions. Ozenoxacin was significantly superior to placebo after 5 days of therapy, with clinical success rates of 54.4% and 37.9%, respectively (*P*=0.001).[21] Ozenoxacin also demonstrated superior microbiological success compared with placebo after 2 days of therapy (87.2% vs 63.9%; *P*=0.002). Ozenoxacin was well tolerated: 8 of 206 patients experienced AEs, with only 1 of these patients experiencing an adverse event (rosacea and seborrheic dermatitis) that was considered at least potentially related to the study treatment; none were serious.[21]

A subsequent pooled analysis of individual patient data from both phase 3 trials in patients with impetigo treated with ozenoxacin (n = 361) or placebo (n = 362) confirmed the superior clinical success of ozenoxacin versus vehicle after 5 days of therapy and the superior microbiological success of ozenoxacin versus vehicle after 2 days of therapy. The analysis concluded that ozenoxacin showed superior clinical and microbiological responses compared with vehicle in children as young as 2 months of age and in adults with impetigo.[23]

More recent comparative and pooled analyses further support the efficacy and safety of ozenoxacin in impetigo management. A comparative study (2023) evaluated the safety, bacteriological efficacy, and clinical outcomes of 1% ozenoxacin cream against 2% mupirocin cream following a 7-day treatment period for pediatric impetigo patients (n=33). Ozenoxacin demonstrated more rapid clinical improvement than mupirocin after 4 days of therapy (8/16 vs 2/17; *P*=0.038). Ozenoxacin also demonstrated superior clinical (14 of 16 vs 13 of 17) and microbiological (15 of 16 vs 14 of 17) success as compared with mupirocin, after 7 days of therapy. Both treatments were well tolerated, with 1 mild application-site AE reported in the mupirocin group.[24] Furthermore, a systematic review and meta-analysis of RCTs comparing ozenoxacin 1% with placebo or mupirocin found that ozenoxacin 1% significantly improved clinical and micro-biological success rates and reduced treatment failure compared with placebo in patients with impetigo. Efficacy was comparable to mupirocin, although the estimates were less precise.[25]

Taken together, these results highlight that topical ozenoxacin can effectively treat impetigo with a low risk of AEs and low risk of resistance development.[1,6] In light of the emerging resistance to fusidic acid and mupirocin, ozenoxacin cream may be a valuable addition to the antibacterial arsenal for treating impetigo,[1] both as a first-line topical agent for impetigo and as a second-line agent in mupirocin failures.

**Limitations**

Antimicrobial resistance patterns, particularly for topical agents, vary by geographic region, which may limit the generalizability of findings. In addition, the evidence base for newer topical therapies continues to evolve; long-term data on resistance patterns and comparative effectiveness remain limited. Literature specifically addressing stewardship-informed strategies in impetigo is also scarce. To address this gap and provide practical guidance, the recommendations presented here are informed by both the available evidence and advisors' experience and opinion.

## CONCLUSION

Impetigo is a highly contagious dermatologic condition that is frequently treated with antibiotics, making it an important target for antimicrobial stewardship. While treatment remains necessary to limit transmission and improve patient outcomes, increasing resistance to commonly used topical agents highlights the limitations of current management strategies. Appropriate treatment selection, avoidance of unnecessary antibiotic use, and consideration of resistance patterns are needed to optimize outcomes while preserving antibiotic effectiveness. In this context, topical ozenoxacin, which has a low capacity for developing resistance and acts against organisms resistant to other topical agents, may help address existing gaps and support antibiotic stewardship-informed care.

## DISCLOSURES

For the research of this work, an educational grant was received from Pelthos Therapeutics.

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Nanette Silverberg MD is a consultant, advisor, or investigator for AbbVie, Avita, Incyte, Pelthos, Pfizer, Regeneron, Sanofi, and Verrica Pharmaceuticals.

## REFERENCES

1. Vila J, Hebert AA, Torrelo A, et al. Ozenoxacin: a review of preclinical and clinical efficacy. *Expert Rev Anti Infect Ther.* 2019;17(3):159-168. doi:10.1080/14787210.2019.1573671
2. Schachner L, Andriessen A, Bhatia N, Grada A, Patele D. Topical ozenoxacin cream 1% for impetigo: a Review. *J Drugs Dermatol.* 2019;18(7):655-661.
3. Schachner LA, Andriessen A, Benjamin LT, et al. Do Antimicrobial resistance patterns matter? An algorithm for the treatment of patients with impetigo. *J Drugs Dermatol.* 2021;20(2):134-142. doi:10.36849/JDD.5745
4. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;59(2):e10-e52. doi:10.1093/cid/ciu296
5. Oganesyan A, Sivesind T, Dellavalle R. From the Cochrane Library: interventions for impetigo. *JMIR Dermatology.* 2021;4(2):e33433. doi:10.2196/33433
6. Schachner LA, Lynde CW, Kircik LH, et al. Treatment of impetigo and antimicrobial resistance. *J Drugs Dermatol.* 2021;20(4):366-372. doi:10.36849/JDD.2021.5795
7. van Bijnen EME, Paget J, den Heijer CDJ, et al. Evidence-based primary care treatment guidelines for skin infections in Europe: A comparative analysis. *Eur J Gen Pract.* 2014;20(4):294-300. doi:10.3109/13814788.2013.872621
8. National Eczema Society. Skin infections and eczema. National Eczema Society. Accessed April 5, 2026. https://eczema.org/information-and-advice/living-with-eczema/skin-infections-and-eczema/
9. Schachner LA, Torrelo A, Grada A, et al. Treatment of impetigo in the pediatric population: consensus and future directions. *J Drugs Dermatol.* 2020;19(3):281-290. PMID: 32550690.
10. González-López A, Selmer M. Mechanisms of fusidic acid resistance. *Biochem Soc Trans.* 2025;53(4):1011-1022. doi:10.1042/BST20253064
11. Koning S, van der Sande R, Verhagen AP, et al. Interventions for impetigo. *Cochrane Database Syst Rev.* 2012;2012(1):CD003261. doi:10.1002/14651858.CD003261.pub3
12. Rodrigues J, Sá K, Lopes G, Piovesan M, Santos E, Martimbianco AL. Meta-research study on the quality of randomized controlled trials evaluating drug therapy for impetigo. *Dermatol Pract Concept.* 2025;15(4):5668. doi:10.5826/dpc.1504a5668
13. World Health Organization. Antimicrobial resistance. 2023. Accessed April 4, 2026. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
14. Lim JS, Park HS, Cho S, Yoon HS. Antibiotic susceptibility and treatment response in bacterial skin infection. *Annals of Dermatology.* 2018;30(2):186-191. doi:10.5021/ad.2018.30.2.186
15. McNeil JC, Hulten KG, Kaplan SL, Mason EO. Mupirocin resistance in staphylococcus aureus causing recurrent skin and soft tissue infections in children. *Antimicrob Agents Chemother.* 2011;55(5):2431-2433. doi:10.1128/AAC.01587-10
16. Van Bambeke F, Glupczynski Y, Mingeot-Leclercq MP, Tulkens P. Mechanisms of action - retapamulin. In: I*nfectious Diseases*. 3rd ed. 2010. Accessed April 5, 2026. https://www.sciencedirect.com/topics/medicine-and-dentistry/retapamulin
17. Gibbons JA, Smith HL, Kumar SC, et al. Antimicrobial stewardship in the treatment of skin and soft tissue infections. *Am J Infect Control.* 2017;45(11):1203-1207. doi:10.1016/j.ajic.2017.05.013
18. D'Cunha NM, Peterson GM, Baby KE, Thomas J. Impetigo: A need for new therapies in a world of increasing antimicrobial resistance. *J Clin Pharm Ther.* 2018;43(1):150-153. doi:10.1111/jcpt.12639
19. van Duijn PJ, Bonten MJ. Antibiotic rotation strategies to reduce antimicrobial resistance in Gram-negative bacteria in European intensive care units: study protocol for a cluster-randomized crossover controlled trial. *Trials.* 2014;15:277. doi:10.1186/1745-6215-15-277
20. Primhak S, Gataua A, Purvis D, et al. Treatment of Impetigo with Antiseptics—Replacing Antibiotics (TIARA) trial: a single blind randomised controlled trial in school health clinics within socioeconomically disadvantaged communities in New Zealand. *Trials.* 2022;23:108. doi:10.1186/s13063-022-06042-0
21. Rosen T, Albareda N, Rosenberg N, et al. Efficacy and safety of ozenoxacin cream for treatment of adult and pediatric patients with impetigo: a randomized clinical trial. *JAMA Dermatol.* 2018;154(7):806-813. doi:10.1001/jamadermatol.2018.1103
22. Gropper S, Albareda N, Chelius K, et al. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. *Future Microbiol.* 2014;9(9):1013-1023. doi:10.2217/fmb.14.78
23. Hebert AA, Albareda N, Rosen T, et al. Topical antibacterial agent for treatment of adult and pediatric patients with impetigo: pooled analysis of phase 3 clinical trials. *J Drugs Dermatol.* 2018;17(10):1051-1057.
24. Dash P, Khan F, Sarda S, Tanwar R. A comparative study of topical 1% ozenoxacin cream and 2% mupirocin cream for the treatment of impetigo in children. *Dermatol Pract Concept.* 2025 Oct 1;15(4):e20255668.
25. Tuesta BL, Arones-Santayana CA, Sáenz GAV, et al. Ozenoxacin 1% in pediatric and adult patients with impetigo: a meta-analysis of randomized trials. *JCM.* 2025;14(7):2157. doi:10.3390/jcm14072157

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Increased Risk of Skin Cancers in Certain Occupations

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## ABSTRACT

Ultraviolet radiation (UVR) is the main risk factor for the development of skin cancer, and outdoor workers are especially at risk. Despite this, there is a lack of educational programs, and preventative measures are seldom implemented to protect these workers. This review discusses the various occupational causes of skin cancer as well as the need for increased skin surveillance and public health campaigns. Occupational exposures such as UVR, chemicals, and pesticides increase the risk of skin cancer. Examining the various occupational risks of skin cancers highlights the need for enhanced surveillance, prevention, education, and public health initiatives for these workers. Dermatologists are urged to tackle these issues to improve outcomes for these individuals.

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## INTRODUCTION

The incidence of melanoma and non-melanoma skin cancer (NMSC) has been increasing worldwide.[1] NMSC mainly consists of keratinocyte skin cancer, with about 80% basal cell carcinoma (BCC) and about 20% squamous cell carcinoma (SCC).[2] Studies have shown that 65 to 90% of all skin cancers are attributable to solar ultraviolet radiation (UVR) exposure.[3,4]

This exposure can be impacted by certain occupations. Pega et al found that globally in 2019, 1.6 billion workers were occupationally exposed to UVR. They also found that over 2000–2019, attributable deaths and disability-adjusted life years almost doubled.[5] Bauer et al found that participants with high occupational ultraviolet (UV) exposure had a greater than two-fold increased risk of developing BCC in commonly UV-exposed body sites compared to participants with no or moderate occupational UV exposure.The risk in individuals with occupational exposure increases independently of histological subtype, tumor localization, and Fitzpatrick phototype.[6] Keim et al conducted a population-based cohort study of 1621 subjects, with no previous keratinocyte carcinoma (KC), who were followed up to sixteen years.They found that 21% of the patients developed one KC, and 47% of those patients developed at least 2 KCs.[7] Also, there have been several studies reporting the coexistence of different types of KC, melanoma, and premalignant lesions in the same individual.[8] Rarely, malignant melanoma has been found within BCC and SCC.[9] Another significant risk factor is chemical exposure.

Our review aims to provide a comprehensive overview of occupational risks of skin cancers, highlighting the importance of skin surveillance and public health campaigns.

### Occupations

*Welder*

Globally, there are about 11 million welders and an estimated 110 million additional workers who obtain welding-related exposures. The latter may be employed in fields such as construction, farming, shipbuilding, or vehicle servicing.[10] Arc welding exposes individuals to the full range of UVR, including UVA, UVB, and UVC radiation, as well as fumes, gases, and co-exposures to asbestos and solvents.[11] While the association between welding and skin cancer is still being studied, the International Agency for Research on Cancer (IARC) classified UVR and fumes from arc welding as Group 1 or 'carcinogenic to humans' in 2017.[10]

Ocular melanoma is a well-recognized risk linked to UVR exposure from welding. Case-control studies have shown positive associations with risks persisting after adjusting for sun exposure, sunbed use, or both. A dose–response relationship with job duration was also observed.[12] Other case-control studies looked to see the association of welding with NMSC. Heltoft et al examined a cohort of 4333 metal arc welders who were followed for 25 years, and they found a significantly increased risk of BCC in the head and neck region of welders compared with controls.[11] Most other case-control studies did not find an increased prevalence of skin cancer in welders,

but this may be due to limitations such as a small sample size and a young average age of welders. In Emmett et al's study, they investigated 158 workers with a mean age of 43 years.[13] In addition to increased UVR exposure, chronic skin trauma and chronic inflammation from welding burns may also play a role in the development of skin cancer. Donoghue et al. reported a case of BCC occurring at a site of previous episodes of welding-induced cutaneous erythema and skin peeling.[14]

*Farmer*

Farmers are at a particularly high risk of developing skin cancer due to their constant exposure to UVR and pesticides. One study found that farmers made up 33% of all BCC patients, with the nose and cheek being the most common areas affected.[15] Another study showed that 27% of farmers had a recurrence of the disease, compared to 12% in non-farmers.[15]

Arsenic-based pesticides are particularly harmful to farmers, leading to conditions like Bowen's disease, multiple BCCs, and SCCs. Non-arsenic pesticides, such as paraquat, are also potentially carcinogenic.[16]

*Firefighter*

Research has shown that despite wearing protective gear, firefighters are still vulnerable because the UV protection provided by their gear is often inadequate, and their work involves prolonged outdoor activities.[17,18] Firefighters also face risks from polycyclic aromatic hydrocarbons (PAHs), benzene, and polychlorinated biphenyls (PCBs). Studies have revealed that after responding to fires, firefighters often have significantly higher levels of PAHs on their skin, highlighting the elevated risk of skin cancer in this profession.[17-19]

The risk of developing melanoma is particularly high among firefighters, and a systematic review of case-control studies found that male firefighters are more likely to develop melanoma compared to the general population, with a standardized morbidity odds ratio of 1.5 (95% CI: 1.33-1.70).[17] Another study found that firefighters have a higher risk of melanoma than police officers.[19,20]

*Pilot*

Pilots are regularly exposed to significant levels of UVA radiation during flights. While aircraft windshields are designed to block UVB radiation, they still allow a substantial amount of UVA radiation to pass through, with transmission rates ranging from 0.41% to 53.5%.[21] Research has shown that pilots flying at 30,000 feet for about 56.6 minutes receive the same amount of UVA radiation as they would during a 20-minute session in a tanning bed.[21] Pilots are also exposed to higher doses of cosmic radiation at high altitudes. Studies have found that commercial airline pilots have a standardized incidence ratio of 1.80 for non-melanoma skin cancer due to cosmic radiation exposure.[22]

Pilots face a higher risk of melanoma due to their exposure to UVA radiation and possibly cosmic radiation. A meta-analysis found that pilots and cabin crew have a higher incidence of melanoma, with a standardized incidence ratio of 2.22 for civil pilots.[21,22] For NMSC, risk factors among pilots include having an at-risk skin type, a history of childhood sunburns, a family history of NMSC, and extended flight time at high latitudes. Pilots who have flown for 20 years or more are at an increased risk of developing NMSC, with an odds ratio of 1.4 associated with flight time at high latitudes.[23]

*Veteran*

Veterans who have been deployed in desert climates, such as Iraq and Afghanistan, face a high risk of skin cancer. Research has shown that 77% of veterans spent 4 or more hours per day in direct sunlight, and 63% of these veterans reported experiencing at least one sunburn during their deployment.[24] Ethnic background also plays a role in the risk of developing NMSC among veterans. Those of Irish, Welsh, Scottish, or English descent, along with veterans showing signs of solar damage like actinic keratosis and solar elastosis, are at higher risk. Actinic keratosis on the face and solar elastosis on the neck have been identified as key predictors of skin cancer in this group.[25]

Studies indicate that veterans with actinic keratosis, solar elastosis, and prolonged sun exposure are more likely to develop NMSC than the general population.[25] Additionally, a study found that veterans with a history of multiple BCCs had a 40% chance of developing another within two years, which highlights the importance of regular follow-up visits for early detection and treatment.[26]

*Construction*

Thomas et al used an ecological model to examine melanoma incidence in construction workers. They found that in US counties with lower UVR, there is an association between high proportions of construction workers and melanoma incidence rates. In higher UV counties, melanoma incidence was consistently elevated across all occupation proportions, indicating occupation may not exert a significant impact at higher ultraviolet exposure levels.[27] Peters et al also looked at UVR exposure and found 6.31% (4556 cases) of NMSC cases were estimated to be attributable to occupational exposure, the majority of which in construction fields, to solar UVR.[28]

*Chemical Worker*

Nonsolar factors are also important with regard to causing NMSC. Gallagher et al conducted a case-control study and found elevated risks for SCC in subjects exposed to insecticides, herbicides, fungicides and seed treatments, petroleum products, grease, and several other exposures. This group also found increased risks of BCC in subjects exposed to fiberglass dust.[29]

Benzene exposure can occur in various fields such as petroleum, chemical production, printing, and rubber manufacturing. In 2017, the IARC confirmed the carcinogenicity of benzene based on evidence in experimental animals and humans.[30] Stenehjem et al examined a cohort of offshore petroleum workers and found an association between exposure to crude oil or benzene and skin cancer risk on hands and forearms.[31] Lastly, arsenic exposure has been associated with an increased risk for all types of skin cancer.[32]

*Lifeguards and maritime workers*

Research has shown that lifeguards have a high frequency of sunburns.[33] In addition, many lifeguards believe that a tan makes people more attractive, which contributes to higher UVR exposure. Even after participating in a sun safety program, this belief did not significantly change, showing how deeply rooted these attitudes are.[33] Maritime workers are also at higher risk of cancers due to UVR exposure, including mesothelioma and non-melanoma skin cancer, most notably lip cancer.[34]

## DISCUSSION

Standard prevention strategies like wearing sunscreen, protective clothing, taking shade, and getting regular skin checks are critical for workers. The Occupational Safety and Health Administration (OSHA) tackles sun protection for outdoor workers, specifically those in general industry, maritime, and construction, through its regulations regarding personal protective equipment (PPE), though the use of sunscreen is not explicitly mentioned. OSHA requires employers to provide eye, face, foot, and hand protection as well as filter lenses with the appropriate associated shade number for affected employees.[35] In regard to welders, OSHA states that helmets and hand shields that protect the face, neck, and ears from direct radiant energy be provided. OSHA also states that where permitted, welders should be enclosed in individual booths or noncombustible screens painted with finishes of low reflectivity such as zinc oxide and lamp black.[36]

Despite this, adherence can be inconsistent. One study found that welders may not wear their protective gear due to the work environment being too hot and the gear itself being more of a hindrance when working jobs requiring more detailed welds.[37] Even in welders who use protective gear, the UVR from the welding light can be reflected off painted walls and ceilings.[38] Workers' decisions to use sunscreen in addition to PPE are also variable. For example, a study showed that only 44.3% of outdoor workers regularly used sunscreen compared to 60.2% of indoor workers.[39] Cioffi et al found that 25% of construction workers reported rarely or never using sunscreen, while Laporte et al found 92% of construction workers reported this.[40,41] This highlights the need for more effective education on sun protection practices and the importance of regular skin exams for early detection of skin cancers.

The Firefighter Cancer Initiative (FCI) addresses occupational risks by promoting regular skin cancer screenings and encouraging better sun protection habits. The initiative also focuses on reducing carcinogen exposure by recommending thorough decontamination of personal protective equipment (PPE) to limit skin absorption of hazardous chemicals. Additionally, FCI uses innovative tools like skin swabs and silicone wristbands to monitor toxic exposures during firefighting operations.[17]

Previous public health campaigns have been instrumental in raising awareness. The Slip! Slop! Slap! Campaign, launched in Australia in 1981, encouraged sun safety by promoting the use of shirts, sunscreen, and hats. This campaign later added messages about seeking shade and wearing sunglasses, making it one of the most successful efforts to reduce skin cancer risks.[42]

In addition to basic sun protection methods, setting up shaded rest areas and adjusting work hours to avoid the strongest midday sun can make a big difference.[43] Heydari et al also investigated the implementation of a mobile phone-based text message intervention among a sample of seafarers, and found significantly higher scores among the intervention group compared to the control group in adopting skin cancer preventive behaviors, perceived self-efficacy, protection motivation, and fear.[44]

Beyond workplace conditions, other factors that may be involved in these occupations may also play a role in skin cancer risk. Kricker et al found that UVR exposure is correlated with increased prevalence of β-HPV, and other studies have shown a correlation between UVR and cutaneous beta human papillomaviruses (β-HPV), specifically in the development of SCC.[45,46] Additionally, having a family history of skin cancer can also increase the risk, suggesting that genetics may play a role. For example, inherited mutations in genes such as CDKN2A, CDK4, POT1, and TERT confer a 60% to 90% lifetime risk of melanoma.[47] Lastly, the risk of skin cancer increases with age due to accumulated sun exposure.[48]

The American Academy of Dermatology is in a strong position to expand these efforts by leading educational campaigns and can collaborate with local health departments to organize free skin cancer screenings at worksites. Dermatologists can collaborate with employers to establish workplace policies promoting regular skin exams and sun protection, such as distributing sunscreen and providing protective clothing. Workplace education on sun protection practices has been seen as workplace support which encourages workers to engage in these protective behaviors.[49] These interventions can significantly reduce the incidence of occupational skin cancers and ensure earlier detection, improving outcomes for those at risk.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

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## REFERENCES

1. Global Burden of Disease 2019 Cancer Collaboration, Kocarnik JM, Compton K, et al. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *JAMA Oncol.* 2022;8(3):420-444. doi:10.1001/jamaoncol.2021.6987.
2. Leiter U, Keim U, Garbe C. Epidemiology of skin cancer: update 2019. *Adv Exp Med Biol.* 2020;1268:123-139. doi:10.1007/978-3-030-46227-7_6.
3. Koh HK, Geller AC, Miller DR, et al. Prevention and early detection strategies for melanoma and skin cancer: current status. *Arch Dermatol.* 1996;132(4):436-443.
4. Glanz K, Buller DB, Saraiya M. Reducing ultraviolet radiation exposure among outdoor workers: state of the evidence and recommendations. *Environ Health.* 2007;6:22. doi:10.1186/1476-069X-6-22.
5. Pega F, Momen NC, Streicher KN, et al. Global, regional and national burdens of non-melanoma skin cancer attributable to occupational exposure to solar ultraviolet radiation for 183 countries, 2000-2019: a systematic analysis from the WHO/ILO Joint Estimates of the work-related burden of disease and injury. *Environ Int.* 2023;181:108226. doi:10.1016/j.envint.2023.108226.
6. Bauer A, Haufe E, Heinrich L, et al. Basal cell carcinoma risk and solar UV exposure in occupationally relevant anatomic sites: do histological subtype, tumor localization, and Fitzpatrick phototype play a role? A population-based case-control study. *J Occup Med Toxicol.* 2020;15:28. doi:10.1186/s12995-020-00279-8.
7. Keim U, van der Pols JC, Williams GM, et al. Exclusive development of a single type of keratinocyte skin cancer: evidence from an Australian population-based cohort study. *J Invest Dermatol.* 2015;135(3):728-733. doi:10.1038/jid.2014.410.
8. Suhonen V, Siiskonen H, Suni M, et al. Malignant and in situ subtypes of melanoma are associated with basal and squamous cell carcinoma and its precancerous lesions. *Eur J Dermatol.* 2022;32(2):187-194. doi:10.1684/ejd.2022.4221.
9. Cornejo KM, Deng AC. Malignant melanoma within squamous cell carcinoma and basal cell carcinoma: is it a combined or collision tumor?—A case report and review of the literature. *Am J Dermatopathol.* 2013;35(2):226-234. doi:10.1097/DAD.0b013e3182545e27.
10. Guha N, Loomis D, Guyton KZ, et al. Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. *Lancet Oncol.* 2017;18(5):581-582. doi:10.1016/S1470-2045(17)30255-3.
11. Heltoft KN, Slagor RM, Agner T, et al. Metal arc welding and the risk of skin cancer. *Int Arch Occup Environ Health.* 2017;90(8):873-881. doi:10.1007/s00420-017-1248-5.
12. Guénel P, Laforest L, Cyr D, et al. Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. *Cancer Causes Control.* 2001;12(5):451-459. doi:10.1023/a:1011271420974.
13. Emmett EA, Buncher CR, Suskind RB, Rowe KW Jr. Skin and eye diseases among arc welders exposed to welding operations. *J Occup Med.* 1981;23(2):85-90. doi:10.1097/00043764-198102000-00010.
14. Donoghue AM, Sinclair MJ. Basal cell carcinoma after frequent episodes of cutaneous erythema and peeling induced by welding. *Occup Environ Med.* 1999;56(9):646. doi:10.1136/oem.56.9.646a.
15. Szewczyk M, Pazdrowski J, Golusiński P, et al. Basal cell carcinoma in farmers: an occupation group at high risk. *Int Arch Occup Environ Health.* 2016;89(3):497-501. doi:10.1007/s00420-015-1088-0.
16. Spiewak R. Pesticides as a cause of occupational skin diseases in farmers. *Ann Agric Environ Med.* 2001;8(1):1-5.
17. Caban-Martinez AJ, Hughes J, Bator C. A Total Worker Health approach to skin exposure assessment: experiences from the Firefighter Cancer Initiative. *Ann Work Expo Health.* 2021;65(2):143-147. doi:10.1093/annweh/wxaa066.
18. Hoppe-Jones C, Griffin SC, Gulotta JJ, et al. Evaluation of fireground exposures using urinary PAH metabolites. *J Expo Sci Environ Epidemiol.* 2021;31(5):913-922. doi:10.1038/s41370-021-00311-.
19. Sama SR, Martin TR, Davis LK, et al. Cancer incidence among Massachusetts firefighters, 1982-1986. *Am J Ind Med.* 1990;18(1):47-54. doi:10.1002/ajim.4700180106.
20. Kang D, Davis LK, Hunt P, et al. Cancer incidence among male Massachusetts firefighters, 1987-2003. *Am J Ind Med.* 2008;51(5):329-335. doi:10.1002/ajim.20549.
21. Sanlorenzo M, Vujic I, Posch C, et al. The risk of melanoma in pilots and cabin crew: UV measurements in flying airplanes. *JAMA Dermatol.* 2015;151(4):450-452. doi:10.1001/jamadermatol.2014.4643.
22. Wilkison BD, Wong EB. Skin cancer in military pilots: a special population with special risk factors. *Cutis.* 2017;100(4):218-220.
23. Nicholas JS, Swearingen CJ, Kilmer JB. Predictors of skin cancer in commercial airline pilots. *Occup Med (Lond).* 2009;59(6):434-436. doi:10.1093/occmed/kqp058.
24. Powers JG, Patel NA, Powers EM, et al. Skin cancer risk factors and preventative behaviors among United States military veterans deployed to Iraq and Afghanistan. *J Invest Dermatol.* 2015;135(11):2871-2873. doi:10.1038/jid.2015.238.
25. Rigopoulos D, Petropoulou H, Nikolopoulou M, et al. Total congenital anonychia in two children of the same family. *J Eur Acad Dermatol Venereol.* 2006;20(7):894-896. doi:10.1111/j.1468-3083.2006.01585.x.
26. Beatson M, Misitzis A, Landow S, et al. Predictors of basal cell carcinoma and implications for follow-up in high-risk patients in the Veterans Affairs Keratinocyte Carcinoma Chemoprevention (VAKCC) Trial. *J Cutan Med Surg.* 2021;25(1):102-103. doi:10.1177/1203475420945230.
27. Thomas KM, Cullison CR, Herrera HO, et al. Occupational association with melanoma: a US ecological county-level analysis. *Arch Dermatol Res.* 2024;316(5):165. doi:10.1007/s00403-024-02922-4.
28. Peters CE, Kim J, Song C, et al. Burden of non-melanoma skin cancer attributable to occupational sun exposure in Canada. *Int Arch Occup Environ Health.* 2019;92(8):1151-1157. doi:10.1007/s00420-019-01454-z.
29. Gallagher RP, Bajdik CD, Fincham S, et al. Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev.* 1996;5(6):419-424.
30. Loomis D, Guyton KZ, Grosse Y, et al. Carcinogenicity of benzene. *Lancet Oncol.* 2017;18(12):1574-1575. doi:10.1016/S1470-2045(17)30832-X.
31. Stenehjem JS, Robsahm TE, Brâtveit M, et al. Aromatic hydrocarbons and risk of skin cancer by anatomical site in 25,000 male offshore petroleum workers. *Am J Ind Med.* 2017;60(8):679-688. doi:10.1002/ajim.22741.
32. Kennedy C, Bajdik CD, Willemze R, et al. Chemical exposures other than arsenic are probably not important risk factors for squamous cell carcinoma, basal cell carcinoma, and malignant melanoma of the skin. *Br J Dermatol.* 2005;152(1):194-197. doi:10.1111/j.1365-2133.2005.06411.x.
33. Hiemstra M, Glanz K, Nehl E, et al. Changes in sunburn and tanning attitudes among lifeguards over a summer season. *J Am Acad Dermatol.* 2012;66(3):430-437.
34. Ugelvig Petersen K, Pukkala E, Martinsen JI, et al. Cancer incidence among seafarers and fishermen in the Nordic countries. *Scand J Work Environ Health.* 2020;46(5):461-468. doi:10.5271/sjweh.3879.
35. Occupational Safety and Health Administration. 1910.133 - Eye and face protection. Accessed February 4, 2025. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.133.
36. Occupational Safety and Health Administration. 1910.252 - General requirements. Accessed February 4, 2025. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.252.
37. Dixon AJ, Dixon BF. Ultraviolet radiation from welding and possible risk of skin and ocular malignancy. *Med J Aust.* 2004;181(3):155-157. doi:10.5694/j.1326-5377.2004.tb06207.x.
38. Falcone L. Welding fume exposure and lung cancer: Evidence of lung toxicity and tumor promotion from in vivo studies in A/J mice. West Virginia University; 2018. doi:10.33915/etd.5567.
39. Trakatelli M, Barkitzi K, Apap C, et al. Skin cancer risk in outdoor workers: a European multicenter case-control study. *J Eur Acad Dermatol Venereol.* 2016;30 Suppl 3:5-11. doi:10.1111/jdv.13603.
40. Cioffi J, Wilkes L, O'Brien J. Outdoor workers and sun protection: knowledge and behaviour. *Constr Econ Build.* 2002;2(2):10-14.
41. Laporte J. Sensibilisation des salariés du bâtiment et des travaux publics au risque solaire: pour une prévention efficace. *Arch Mal Prof Env.* 2006;67(6):828-841. doi:10.1016/S1775-8785(06)70486-6.
42. Smit-Kroner C, Brumby S. Farmers sun exposure, skin protection and public health campaigns: An Australian perspective. *Prev Med Rep.* 2015;2:602-607. Published 2015 Jul 22. doi:10.1016/j.pmedr.2015.07.004.
43. Cherrie JW, Cherrie MPC. Workplace exposure to UV radiation and strategies to minimize cancer risk. *Br Med Bull.* 2022;144(1):45-56. doi:10.1093/bmb/ldac019.
44. Heydari E, Dehdari T, Solhi M, et al. Can adopting skin cancer preventive behaviors among seafarers be increased via a theory-based mobile phone-based text message intervention? A randomized clinical trial. *BMC Public Health.* 2021;21(1):134. Published 2021 Jan 14. doi:10.1186/s12889-020-09893-x.
45. Kricker A, Weber MF, Brenner N, et al. High ambient solar UV correlates with greater beta HPV seropositivity in New South Wales, Australia. *Cancer Epidemiol Biomarkers Prev.* 2020;29(1):49-56. doi:10.1158/1055-9965.EPI-19-0400.
46. Tommasino M. HPV and skin carcinogenesis. *Papillomavirus Res.* 2019;7:129-131. doi:10.1016/j.pvr.2019.04.003.
47. Ransohoff KJ, Jaju PD, Tang JY, et al. Familial skin cancer syndromes: Increased melanoma risk [published correction appears in J Am Acad Dermatol. 2016 Jun;74(6):1290. doi: 10.1016/j.jaad.2016.03.032.]. *J Am Acad Dermatol.* 2016;74(3):423-436. doi:10.1016/j.jaad.2015.09.070.
48. Yu SY, Hirsch A, Zaslavsky O, et al. Risk factors and early prevention of skin cancer in rural older outdoor workers: a scoping review. *Geriatr Nurs.* 2023;54:37-45. doi:10.1016/j.gerinurse.2023.08.017.
49. Janda M, Stoneham M, Youl P, et al. What encourages sun protection among outdoor workers from four industries? *J Occup Health.* 2014;56(1):62-72. doi:10.1539/joh.13-0179-oa.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Generative Artificial Intelligence Augmentation of a Clinical Trial of a Dermo-cosmetic Intervention for Acne Remission Maintenance

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## ABSTRACT

**Background:** A practical application of artificial intelligence (AI) in healthcare is to generate artificial datasets that capture the characteristics of a real source dataset without exposing protected health information. This approach is particularly relevant to research settings where recruitment and long-term follow-up are barriers to generating robust clinical evidence.

**Objective:** To describe the protocol of a study incorporating augmented patient datasets to assess the efficacy of a dermo-cosmetic product (Cleanance Comedomed+®) in maintaining acne remission after discontinuation of oral isotretinoin.

**Methods:** In a randomized, placebo-controlled, blinded clinical trial, patients will receive the dermo-cosmetic product or placebo for up to 12 months. Study outcomes are the number of observed relapses and time to first relapse. To overcome recruitment constraints and reach the 400 patients required to ensure sufficient precision for a time-dependent event criterion, a cohort augmentation strategy using artificial data is implemented. The technology relies on generative models of the Riemannian Hamiltonian Variational Autoencoder type, which learn a compact and geometrically structured latent representation of real clinical data. Generation of artificial patients will occur iteratively, and the initial dataset will be progressively enriched as new real inclusions become available. Reliability of generated data will be assessed and validated through human oversight using quantitative and qualitative metrics covering 4 dimensions: (1) statistical fidelity; (2) diversity and utility; (3) confidentiality; and (4) clinical plausibility.

**Discussion and Conclusion:** Structured integration of artificial data into this clinical trial illustrates the potential of generative AI as a methodological tool complementing conventional approaches in clinical research.

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## INTRODUCTION

Generative artificial intelligence (AI) is increasingly being adopted in healthcare settings to accelerate innovation.[1] Realistic artificial datasets can be generated to capture the characteristics of a real source dataset (distributions, non-linear relationships, noise) without exposing protected health information.[2,3] Artificial data can overcome patient recruitment difficulties and mitigate the impact of prolonged follow-up and low-frequency or stochastic events already observed in the real dataset by stabilizing their statistical representation, while providing statistical power equivalent to that obtained with exclusively real data. Probabilistic and generative models have been shown to faithfully reproduce not only marginal distributions, but also multivariate dependencies and certain clinical trajectories observed in limited datasets.[3-7]

The medicalization of dermo-cosmetic products requires the production of robust, comparative, and reproducible clinical evidence. In the setting of recalcitrant moderate to severe acne, systemic treatment with oral isotretinoin remains the therapeutic gold standard.[8,9] However, a substantial proportion of patients relapse after treatment discontinuation,[10,11] underscoring the need to develop effective strategies for the post-isotretinoin maintenance phase. As reasons for relapse are myriad and individual,[11,12] demonstrating the efficacy of dermo-cosmetic

solutions in this context requires lengthy comparative clinical trials with large sample sizes, which are often difficult to recruit.

Here, we describe an innovative methodology intended to address a major bottleneck in dermatological research: the difficulty of recruiting large patient cohorts for long-term follow-up studies. This approach is illustrated by the protocol of a study designed to assess maintenance treatment in post-isotretinoin patients. Notably, integration of blinded clinical validation by expert dermatologists aims to ensure that artificial patient profiles are medically indistinguishable from real patients, thereby bridging the gap between statistical fidelity and clinical reality. Importantly, the protocol recognizes that the use of artificial data in clinical research is interpreted as a methodological support tool rather than as a substitute for real-world clinical evidence, and its outputs must be contextualized within a robust clinical and regulatory framework.

## MATERIALS AND METHODS

### Clinical Trial Design

A randomized, placebo-controlled, blinded clinical trial has been designed to evaluate the efficacy of a dermo-cosmetic product (Cleanance Comedomed+®) in maintaining acne remission after discontinuation of oral isotretinoin. The emulsion contains milk thistle *Silybum marianum* fruit extract and niacinamide, for daily facial use by adolescents and young adults with acne-prone skin. Under strict inclusion criteria, patients are to be randomized into 2 parallel arms to receive the dermo-cosmetic product or placebo (excipient formulation). Treatment duration is planned for up to 12 months. Study outcomes include the number of observed relapses and time to first relapse. Patients with acne relapse will be withdrawn. Acne relapse is defined as investigator-confirmed clinical worsening requiring treatment initiation leading to patient withdrawal, ensuring consistency with routine dermatological practice. To limit inter-observer variability, investigators are to follow harmonized relapse assessment criteria predefined in the study protocol. To ensure compliance with ethical standards and participant rights, the clinical study protocol has been thoroughly reviewed and approved by ethics committees. Study participants will be provided with the necessary information regarding the use of AI on their pseudonymized data.

The statistical power calculation indicated the need to include nearly 400 patients to ensure sufficient precision for a time-dependent event criterion. However, recruitment constraints (inclusion window limited to about 6 months, 1-year follow-up burden, multicenter logistics) were expected to restrict enrollment to around 100 patients, potentially compromising the statistical validity of the study and exposing it to an underpowering risk. Innovative solutions integrating AI were therefore considered. The approach presented here offers a dual advantage: securing the statistical power necessary to detect rare relapse events while minimizing the ethical burden of enrolling additional real patients under placebo-controlled conditions.

### Methodological Integration of Artificial Data

To ensure scientific feasibility of the trial without compromising its methodological rigor, a cohort augmentation strategy using artificial data is implemented. The generative modeling technology was developed by BOTdesign (Toulouse, France) and operationalized within the ORIGA platform. It relies on generative models of the Riemannian Hamiltonian Variational Autoencoder (RHVAE) type, which learn a compact and geometrically structured latent representation of real clinical data.[6,7] Unlike classical generative approaches based on direct sampling from a prior in a Euclidean latent space, RHVAEs model the latent space as a Riemannian manifold whose metric is learned from observed data, enabling improved capture of high-information-density regions.

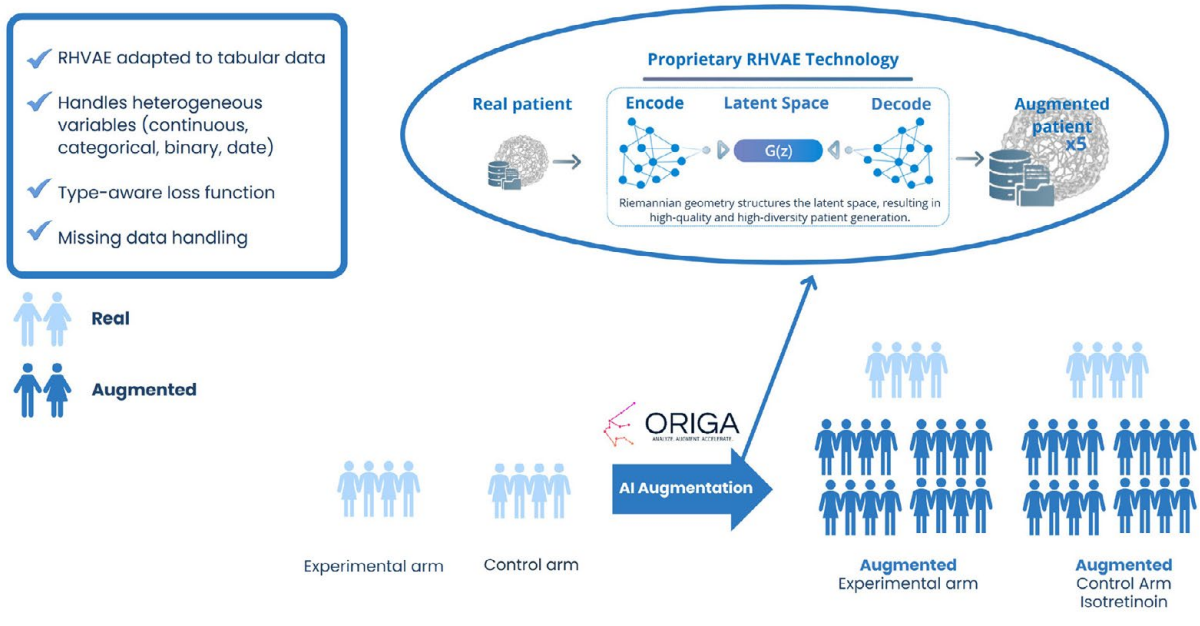
The geometric structuring enables generation of new samples with statistical and clinical characteristics close to those of real patients, without reproducing original individual observations or limiting generation to simple interpolation, thereby contributing to both plausibility and confidentiality. This approach, described as particularly suited to small real cohorts, is relevant in trials with limited sample sizes and time-dependent event criteria, where interindividual variability and censoring (premature withdrawals, relapse leading to discontinuation) can strongly affect statistical power. By employing RHVAE-based models, the study aims to move beyond traditional data interpolation to capture the high-dimensional complexity and non-linear relationships inherent in dermatological clinical trajectories.

Notably, artificial data are used to augment statistical power and enrich patient-level variability for time-to-event modeling under censoring, while preserving the structure learned from real patients. Artificial data do not replace, but complement, real patient observations in primary efficacy or safety analyses.

### Integration Procedure Within the Trial Design

Methodologically, integration of artificial data within the trial is designed as a controlled, balanced, and documented augmentation of both treatment arms (Cleanance Comedomed+® and placebo). In line with the operational organization of the trial, a limited number of real patients are to be enrolled (approximately 50 per arm at initiation of the strategy) according to observed recruitment pace and field constraints; data from these patients will form the initial learning base. For each real patient, 5 artificial patients are to be generated within the corresponding arm (treated or control), resulting in 2 augmented cohorts while preserving the original randomized comparison and avoiding disproportionate amplification of 1 group (Figure 1).

**FIGURE 1.** Use of ORIGA's technology in clinical study design.




Generation of artificial patients is to be carried out iteratively during the study, following an agile project management framework. Once minimum quality and completeness criteria are met, an initial dataset provided to BOTdesign will be progressively enriched as new real inclusions become available. At each stage, the RHVAE model will be adapted using the expanded real database and subsequently used to produce updated artificial cohorts that progressively integrate observed interindividual variability. This adaptive approach aims to limit biases associated with small initial samples, reduce the risk of distributional drift between artificial data and the recruited population, and maintain clinical representativeness over time. The strategy preserves the initial randomization scheme (artificial patients being attached to already randomized arms), maintains balance of clinical covariates by design and, through post-hoc checks, avoids distortion of group comparisons and supports the statistical power of final analyses.

**Statistical, Clinical, and Regulatory Validation**

Emerging requirements of the European regulatory framework and governance principles for AI use in healthcare require that the reliability of generated data be assessed and validated through human oversight using quantitative and qualitative metrics covering 4 dimensions: (1) statistical fidelity; (2) diversity and utility; (3) confidentiality; and (4) clinical plausibility. From the setup phase, BOTdesign's prerequisites are jointly reviewed, test datasets are transmitted to verify technical feasibility, and artificial data deliveries are accompanied by detailed expert reports documenting data quality beyond the mere provision of datasets. Pierre Fabre experts (statistician, AI specialist) contribute to defining acceptance thresholds and interpreting indicators. A dermatologist-based validation methodology is defined in collaboration with BOTdesign to complement quantitative metrics with blinded clinical evaluation.

Within BOTdesign's AI generator, statistical fidelity is assessed using metrics established in the artificial data validation literature.[4,13] Wasserstein distances are calculated variable by variable to quantify the proximity of marginal distributions between real and artificial data, then extended to multivariate analyses to evaluate the preservation of structural relationships among clinical variables. Conditional analyses are planned within clinically relevant subgroups (eg, by initial severity, follow-up characteristics, or risk profiles) to verify that fidelity is maintained not only globally but also within strata critical for clinical interpretation. Statistical moments up to the fourth order are compared in order to capture mean and variance as well as skewness and kurtosis. All indicators must show deviation below 5% compared with real data. This constraint aims to ensure that augmentation does not artificially alter the data structure underlying analyses, particularly those related to relapse timing.

Diversity and utility are assessed to verify that the generator does not merely reproduce or memorize original data and avoids collapse. The width of interquartile ranges and 5% to 95% intervals is compared between real and artificial data, with generated data expected to show wider intervals, interpreted as

evidence of capacity to produce new profiles while remaining within a plausible clinical space. A collapse test across successive generations complements this analysis, aiming to detect any progressive impoverishment of variability during iterative adaptations of the model. Inter-iteration stability is monitored to ensure that enrichment of the real base and model adaptation does not introduce uncontrolled drifts.

Confidentiality is assessed using re-identification risk metrics inspired by the literature.[14] A real observation is considered sufficiently protected if at least 1 artificial data point is closer to it than its own reconstruction by the model. This operational criterion is used to indicate the absence of trivial memorization and the ability of the model to generate plausible synthetic neighbors without replicating original observations. At least 50% of observations are required to meet this criterion, complemented by additional analyses of information leakage or differential privacy-inspired metrics to document a level of protection compatible with confidentiality requirements.

Finally, clinical plausibility of artificial patients is assessed by expert dermatologists through a blinded procedure. Evaluation datasets mix real and artificial profiles, with the proportion of artificial data randomly drawn between 20% and 80% for each assessment batch, and the remainder consisting of real patient data. Practitioners are asked to assess whether profiles are clinically coherent and distinguishable, focusing on intra-patient consistency, plausibility of trajectories across visits, and compatibility of timelines and events. An error rate approaching random classification is considered an indicator of satisfactory clinical indistinguishability, suggesting that artificial data reproduce plausible patient profiles without readily detectable artifacts. This step represents a key translational bridge between AI and clinical dermatology, ensuring that synthetic data are not only statistically valid but also clinically interpretable and coherent with real-life patient trajectories.

## DISCUSSION AND CONCLUSION

This study was conducted in Europe, where the integration of artificial data into clinical research is an emerging topic. Similar to Europe, the United States has also established a regulatory framework guiding the use of AI in healthcare.[15-17] This parallel evolution highlights the importance of situating methodological innovations, such as augmented clinical trials, within both European and American regulatory contexts.

The structured integration of artificial data into this clinical trial illustrates the potential of generative AI as a methodological tool complementing conventional approaches in clinical research, particularly when operational constraints limit real sample size while, concurrently, the nature of the endpoint (relapse), its random occurrence, and follow-up duration require large cohorts. Beyond operational benefits related to recruitment feasibility and timeline optimization, this strategy addresses scientific challenges (statistical power, stability of estimates), ethical considerations (limiting exposure of additional real patients while maintaining balanced augmentation of both arms), and regulatory expectations (traceability, human oversight, validation across fidelity, diversity, confidentiality, and plausibility dimensions), while maintaining a high level of methodological rigor. This approach contributes to the emergence of augmented clinical trial paradigms, particularly relevant in dermo-cosmetic research and, more broadly, in fields where recruitment and long-term follow-up represent major barriers to generating robust clinical evidence. Importantly, conclusions drawn from augmented datasets should always be interpreted in conjunction with real patient data and should not be used in isolation to support clinical or therapeutic recommendations.

## DISCLOSURES

Marco Ardigò has been a consultant and/or speaker and has participated in advisory boards for Almirall, Cantabria, Incyte, Johnson and Johnson, Kyowa Kirin, L'Oreal, Pierre Fabre, Recordati Rare Diseases, SunPharma and Takeda. Luigi Gargiulo has been a consultant and/or speaker and has participated in advisory boards for AbbVie, Almirall, Amgen, BMS, Eli Lilly, Galderma, Incyte, Johnson and Johnson, Novartis, Pfizer, Pierre Fabre, Sanofi, and UCB Pharma. Raphael Fontaine is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Olivier Thuillart is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Jean-Louis Fraysse is an employee of BOTdesign. He declares that the company was responsible for generating the artificial patients as part of this study. The participation of BOTdesign in the study has been funded by Pierre Fabre. Adeline Bacquey is an employee of Pierre Fabre Laboratories who sponsored the study. Pauline Lacoste is an employee of Pierre Fabre Laboratories who sponsored the study. Stéphanie Allassonnière's research is partially funded by the French National Research Agency through the AI Clusters program (grant ANR-21-RHUS-0012) and by the European Union under the ERC Synergy programme (2023–2030), grant agreement No. 101071601 (OCEAN). Aline Stennevin is an employee of Pierre Fabre Laboratories who sponsored the study. Gautier Doat is an employee of Pierre Fabre Laboratories who sponsored the study.

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## REFERENCES

1. Chataut S, Bhatta S, Dahal B, et al. Generative artificial intelligence in healthcare: a systematic review of GANs, diffusion models, large language models, and variational autoencoders for medical applications. *Eur J Appl Sc Eng Technol.* 2025;3(4):182-203.
2. Tucker A, Wang Z, Rotalinti Y, Myles P. Generating high-fidelity synthetic patient data for assessing machine learning healthcare software. *NPJ Digit Med.* 2020;3(1):147.
3. Mendes JM, Barbar A, Refaie M. Synthetic data generation: a privacy-preserving approach to accelerate rare disease research. *Front Digit Health.* 2025;7:1563991.
4. Gonçalves A, Ray P, Soper B, et al. Generation and evaluation of synthetic patient data. *BMC Med Res Methodol.* 2020;20(1):108.
5. D'Amico S, Dall'Olio D, Sala C, et al. Synthetic data generation by artificial intelligence to accelerate research and precision medicine in hematology. *JCO Clin Cancer Inform.* 2023:e2300021.
6. Chadebec C, Thibeau-Sutre E, Burgos N, Allassonnière S. Data augmentation in high dimensional low sample size setting using a geometry-based variational autoencoder. *IEEE Trans Pattern Anal Mach Intell.* 2023;45(3):2879-2896.
7. Ferré F, Allassonnière S, Chadebec C, Minville V. Generating artificial patients with reliable clinical characteristics using a geometry-based variational autoencoder: proof-of-concept feasibility study. *J Med Internet Res.* 2025;27:e63130.
8. Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guideline for the treatment of acne - update 2016 - short version. *J Eur Acad Dermatol Venereol.* 2016;30(8):1261-1268.
9. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2024;90(5):1006.e1-1006.e30.
10. Demirci Saadet E. Investigation of relapse rate and factors affecting relapse after oral isotretinoin treatment in patients with acne vulgaris. *Dermatol Ther.* 2021;34(6):e15109.
11. Lai J, Barbieri JS. Acne relapse and isotretinoin retrial in patients with acne. *JAMA Dermatol.* 2025;161(4):367-374.
12. Tran PT, Berman HS, Leavitt E, et al. Analysis of factors associated with relapse in patients on their second course of isotretinoin for acne vulgaris. *J Am Acad Dermatol.* 2021;84(3):856-859.
13. Eckardt JN, Hahn W, Röllig C, et al. Mimicking clinical trials with synthetic acute myeloid leukemia patients using generative artificial intelligence. *NPJ Digit Med.* 2024;7(1):76.
14. Guillaudeux M, Rousseau O, Petot J, et al. Patient-centric synthetic data generation, no reason to risk re-identification in biomedical data analysis. *NPJ Digit Med.* 2023;6(1):37.
15. American Health Information Management Association (AHIMA). 2024 Artificial Intelligence Regulatory Resource Guide. July 2024. AHIMA Policy & Government Affairs. © 2024 AHIMA.
16. International Comparative Legal Guides (ICLG). Digital Health Laws and Regulations: Artificial Intelligence Tools in Health Services – An Overview of Current and Evolving US Federal and State Health Regulatory Structures 2025-2026. 3 April 2025. Available at: https://iclg.com/practice-areas/digital-health-laws-and-regulations/03-artificial-intelligence-tools-in-health-services-an-overview-of-current-and-evolving-us-federal-and-state-health-regulatory-structures. Accessed 28 January 2026.
17. U.S. Food & Drug Administration (FDA). Artificial Intelligence in Software as a Medical Device. 25 March 2025. Available at: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-software-medical-device. Accessed 28 January 2026.

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# Understanding Skin Sensitivity Across the Body and in Response to Products Using Ecological Momentary Assessment

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## Abstract

Sensitive skin is comprised of a spectrum of symptoms with triggers woven into people's day-to-day lives, making it difficult to fully capture in the lab or with questionnaires relying on people's memory. In the studies described here, we applied an Ecological Momentary Assessment (EMA) approach to capture skin sensitivity as it happens in-life to evaluate: 1) how sensitive skin is distributed across the body, and 2) how sensitive skin responds to product intervention over multiple weeks. We found that women in the US who self-reported sensitive skin experienced a range of skin sensitivity symptoms, most commonly itch, dryness, and redness, but each with a different distribution across body locations. Using EMA, we also found that 2 weeks of regular usage of Dove Sensitive Body Wash (Unilever) in the shower significantly reduced in-life reports of dryness and increased the number of days when women did not report sensitivity compared with usage of a standard sulfate-based cleanser. These studies highlight a novel approach for understanding sensitive skin and assessing treatment efficacy while already demonstrating the importance of a moisturizing skin cleanser as part of such treatment.


Figure 1. Current Dove Sensitive Body Wash.




## The Science and Significance of Skin Sensitivity

Sensitive skin is one of those experiences that most people recognize instantly, but few can define precisely. It might reveal itself as dry and flaking skin, a flush of redness after stepping out into the cold, or a general feeling of tightness and discomfort that doesn't neatly correspond to anything visible on the surface. Dermatologically, it is best understood not as a single condition but as a spectrum of reactions rooted in how the skin protects itself and how it communicates with our brain to form our sensory experiences.[1,2]

At the heart of this experience is the skin barrier, the outermost layer of the skin, made up of tightly packed cells embedded in a matrix of lipids that acts rather like mortar between bricks.[3,4] When this barrier is intact, it holds moisture in and keeps irritants out. When it is compromised, whether through genetics, environmental exposure, overuse of harsh cleansing, or age-related changes, water escapes more easily, and external triggers can penetrate more readily.[5] The result is skin that reacts more quickly and more intensely to things that others might not notice at all. Sitting just beneath this barrier is a dense network of sensory nerve endings. In individuals with sensitive skin, these nerves can become more easily activated, translating everyday stimuli into signals of discomfort, itch, or burning.[6,7]

The triggers themselves are often unremarkable. Temperature swings, hard water, certain fragrances and preservatives, tight or particular fabrics, shaving, and even psychological stress can all provoke a reaction.[8,9] Because these triggers are woven into the fabric of daily life, sensitive skin rarely stays quiet for long, and its expression can shift from day to day and from one part of the body to another. It is also a deeply subjective experience: for example, unusual cold may lead to a bit of dryness in one person, but stinging and irritation in another; and the same person's skin may feel calm one week and reactive the next.[10] Despite this variability, sensitive skin is strikingly common. Across large consumer surveys conducted around the world, roughly half to two-thirds of adults describe their skin as sensitive to some degree, with women reporting it slightly more often than men.[1]

Because the barrier plays such a pivotal role in this story, supporting it is one of the most direct routes to easing sensitivity. Products that support the skin barrier, both moisturizers and gentle cleansers, aim to do exactly that: minimizing disruption to barrier lipids and proteins, replenishing the outer lipid layers of the skin, reinforcing the lipid matrix that holds it together, thereby maintaining the natural retention of moisture.[11] Such product regimens can provide the skin a more resilient surface from which to face its everyday insults, but determining which ones are effective for sensitive skin is a challenge given its subjective and ephemeral nature. That is where our research comes into play.

## Ecological Momentary Assessment for Tracking Skin Sensitivity in Life

Sensitive skin doesn't play by the rules of a lab – a tight, uncomfortable feeling, a hot shower, a persistent itch that appears mid-afternoon, a patch of redness that fades before the day is out. These everyday experiences are fleeting and notoriously difficult to capture with traditional research methods that either rely on often imperfect memory of past sensitivity, or on provoking skin reactions in a lab that do not relate well to people's daily experiences with skin sensitivity.

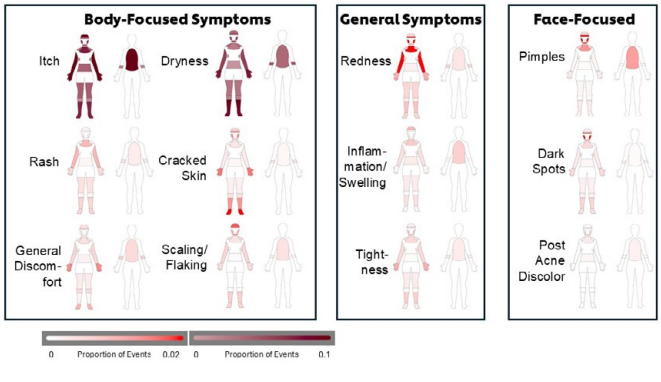
Instead, we have moved to a different approach: Ecological Momentary Assessment (EMA), a method that captures skin sensitivity as it happens in life.[12] Instead of asking people to look back and recall the degree to which their skin felt itchy, irritated, or uncomfortable,[13,14] we invite them to check in with their skin issues at the moment using a simple survey accessible on their mobile devices. The result is a far richer, more accurate picture of skin sensitivity, capturing contextual information such as when symptoms strike, where on the body, and what in daily life seems to set them off. We have run 2 recent studies applying this EMA methodology to the detection and evaluation of intervention on sensitive skin across the body. Participants in both studies reported their skin sensitivity symptoms as they occurred, using a questionnaire available on demand from the home screen on their mobile phones like an app.

In EMA studies, it is critical to maintain engagement with participants. Ideally, we would like the reporting of experienced skin issues to become habitual, but habits take prompting and repetition to develop. We always begin EMA with frequent prompts regarding reporting skin issues during the first few days. Although participants for these studies were recruited because they were experiencing skin sensitivity at study onset, we understood that sensitivity symptoms can come and go, but we nevertheless needed to keep participants not currently experiencing symptoms engaged. Thus, we provided an option for participants to report during the evening hours that they did not experience any skin issues on that day, so they would sustain engagement with the EMA even if their symptoms waned. Anecdotally, we have observed several participants in each of our EMA studies to continue reporting skin issues even after their scheduled participation had ended, an indication of the power of this approach if executed properly.

## Distribution of Skin Sensitivity by Symptoms Across the Body

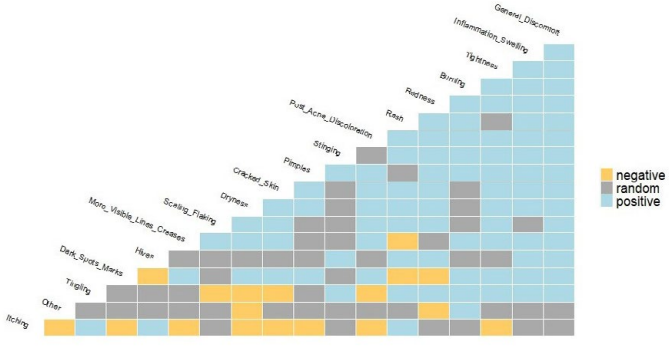
Based on the responses of 117 American women aged 18 to 55 who self-reported skin sensitivity, we found that symptoms associated with sensitive skin manifest across multiple body locations and show substantial variation. We found that the top symptoms reported by the EMA participants were itch and dryness, both occurring with more than twice the frequency of the remaining symptoms. Both symptoms were documented more frequently on locations on the body, particularly hands, arms, feet, and lower legs, than on the face. In fact, we found that most of the top eleven most frequent symptoms in our EMA study, as shown in Figure 2, were more commonly reported on bodily locations other than the face, suggesting key roles for products that are applied all over the body in the management of skin sensitivity.

Figure 2. Prevalence of each issue by body location from EMA reports by women reporting sensitive skin. Issues were grouped as "body-focused" if the top 3 locations by prevalence are on the body, as "face-focused" if the top 3 locations by prevalence are on the face, and as "general" otherwise.




The top 5 symptoms reported during the most intense sensitivity events by participants were general discomfort, rash, stinging, burning, and dryness. Although stinging and burning were not among the top 11 most prevalent symptoms, with each occurring in less than 10% of all reported sensitivity events, their intensity suggests that they are still important symptoms to resolve. We initially found it surprising to see dryness associated with high severity, but we noted that dryness showed high and statistically significant levels of co-occurrence with other sensitivity symptoms such as general discomfort, rash, redness, and inflammation/swelling (see Figure 3). This suggests that, as an indicator of a compromised skin barrier, the occurrence of dry skin may be the precursor to the development of other sensitive skin issues, and moisturizing products should be a part of skin sensitivity prevention and alleviation.

Figure 3. Degree of co-occurrence of sensitive skin symptoms within EMA reports for women reporting sensitive skin. Blue boxes indicate pairs of symptoms that tend to co-occur within the same report, whereas yellow boxes indicate pairs of symptoms where the occurrence of one implies the occurrence of the other is less likely.

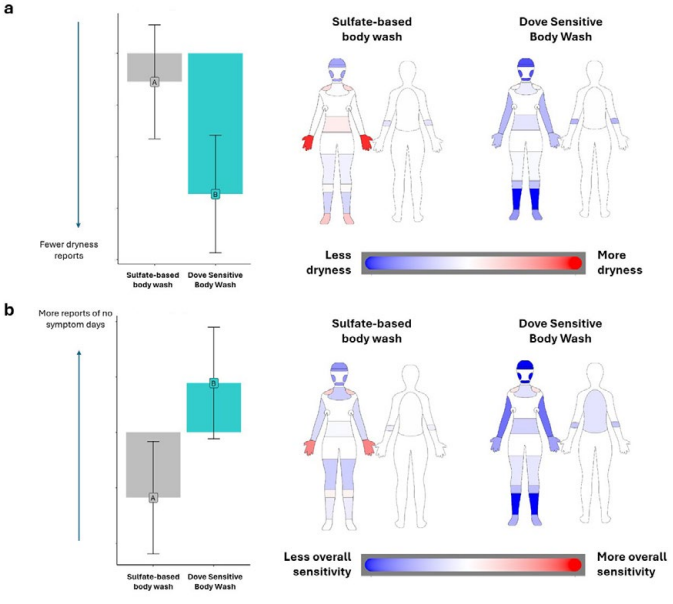



## Incorporating Dove Sensitive Skin Body Wash to Mitigate Body Skin Sensitivity

Dove Sensitive Body Wash is a hypoallergenic and gentle everyday cleanser designed specifically for people with sensitive skin. Formulated with a sulfate-free, mild cleansing blend with 24 hr renewing Micromoisture, Dove Sensitive Body Wash cleanses while protecting the skin barrier.

Our second EMA study evaluated the effectiveness of Dove Sensitive Body Wash for reducing sensitive skin symptoms in everyday life. Following a 2-week baseline period using a standard sulfate-based body wash (control), one group of women was provided with Dove Sensitive Body Wash while another group continued to use the control product, and both groups completed another 2-week test phase while continuing real-time symptom reporting.

Figure 4. (A) Bar chart displaying change in frequency of dryness reports from baseline for each body wash, with error bars indicating 95% confidence intervals. Body heatmaps displaying change in the number of dryness symptoms reported from the baseline phase by each body location and body wash. (B) Bar chart displaying change in the number of "no symptom day" reports from baseline for each body wash, with error bars indicating 95% confidence intervals. Body heatmap displaying change in all skin sensitivity symptoms from the baseline phase for each body location and body wash.




As shown in Figure 4, Dove Sensitive Body Wash led to a significant reduction in the number of dryness events compared with the control cleanser during the test phase, indicating a measurable improvement in that aforementioned "precursor" sensitive skin symptom. Importantly, these reductions were most evident on body locations that our first study identified as being particularly prone to dryness and skin sensitivity in general, including the lower legs, feet, arms, hand, and face, demonstrating that Dove Sensitive Body Wash can support whole-body skin comfort. Beyond symptom-specific improvements, we found a significant increase in reports of "symptom-free" days for the users of Dove Sensitive Body Wash compared with users of the control cleanser.

Taken together, these findings suggest that Dove Sensitive Body Wash minimizes the occurrence of dryness relative to standard cleansers and can actively promote periods of symptom-free skin in real-life conditions. Overall, the application of EMA provided robust real-world evidence that daily cleansing with Dove Sensitive Body Wash contributes to improved skin comfort for individuals with sensitive skin, supporting its role as an effective component of sensitive skin management in everyday life.

## Conclusion

Sensitive skin is common, variable, and personal, but our research using EMA has shown that it can be quantified with contextual detail beyond traditional approaches. In-life reports from women show that skin sensitivity is not confined to the face, but is frequently experienced across the body, with varying distributions of distinct but often interconnected symptoms such as dryness, rash, inflammation, and general discomfort. Our second EMA study extended this understanding by demonstrating that Dove Sensitive Body Wash reduced dryness events and increased symptom-free days under real-life conditions. By helping us understand skin sensitivity with this new level of granularity, we believe EMA can help tailor future approaches for treating sensitive skin for broader populations.

## Disclosure

The work was funded by Unilever Global IP. Unilever provided the commercial products used in the study. JS, MR and BD work for Unilever. Unilever was involved in the collection and analysis of the data.

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## References

1. Farage MA. The prevalence of sensitive skin. *Front Med (Lausanne)*. 2019;6:98.
2. Misery L, Ständer S, Szepietowski JC, et al. Definition of sensitive skin: an expert position paper from the special interest group on sensitive skin of the International Forum for the Study of Itch. *Acta Derm Venereol*. 2017;97(1):4-6.
3. Bosko CA. Skin barrier insights: from bricks and mortar to molecules and microbes. *J Drugs Dermatol*. 2019;18(1 suppl):s63-s67.
4. Del Rosso JQ, Zeichner J, Alexis A, et al. Understanding the epidermal barrier in healthy and compromised skin: clinically relevant information for the dermatology practitioner. *J Clin Aesthet Dermatol*. 2016;9(4 suppl 1):S2-S8.
5. Pinto P, Rosado C, Parreirão C, et al. Is there any barrier impairment in sensitive skin? A quantitative analysis of sensitive skin by mathematical modeling of transepidermal water loss desorption curves. *Skin Res Technol*. 2011;17(2):181-185.
6. Ständer S, Schneider SW, Weishaupt C, et al. Putative neuronal mechanisms of sensitive skin. *Exp Dermatol*. 2009;18(5):417-423.
7. Huet F, Misery L. Sensitive skin is a neuropathic disorder. *Exp Dermatol*. 2019;28(12):1470-1473.
8. Berardesca E, Farage M, Maibach H. Sensitive skin: an overview. *Int J Cosmet Sci*. 2013;35(1):2-8.
9. Duarte I, Silveira JEPS, Hafner MFS, et al. Sensitive skin: review of an ascending concept. *An Bras Dermatol*. 2017;92(4):521-525.
10. Farage MA, Katsarou A, Maibach HI. Sensory, clinical and physiological factors in sensitive skin: a review. *Contact Dermatitis*. 2006;55(1):1-14.
11. Chen B, Tang H, Liu Z, et al. Mechanisms of sensitive skin and the soothing effects of active compounds: a review. *Cosmetics*. 2024;11(6):190.
12. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol*. 2008;4(1):1-32.
13. Corazza M, Guarneri F, Montesi L, Toni G, Donelli I, Borghi A. Proposal of a self-assessment questionnaire for the diagnosis of sensitive skin. *J Cosmet Dermatol*. 2022;21(6):2488-2496.
14. Misery L, Jean-Decoster C, Mery S, et al. A new ten-item questionnaire for assessing sensitive skin: the Sensitive Scale-10. *Acta Derm Venereol*. 2014;94(6):635-639.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Practical Algorithm Guiding Seborrheic Dermatitis Treatment in Adults and Adolescents: New Evidence and Consensus Expert Opinion

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## ABSTRACT

**Background:** Seborrheic dermatitis (SD) is a common, chronic inflammatory skin disease characterized by greasy, scaly plaques on the scalp or body, often with pruritus and impaired quality of life. The pathogenesis involves dysbiosis, including *Malassezia colonization*, excess sebum production, and immune dysregulation with Th17/Th22 activation. Although therapy historically targeted *Malassezia*, growing evidence supports anti-inflammatory strategies.

**Methods:** A systematic literature review identified current treatments and management strategies for SD. Of 399 articles screened, 77 met inclusion criteria and informed algorithm development. A draft algorithm was created from these data and refined through a virtual workshop with 6 board-certified dermatologists and 1 physician assistant.

**Results:** Experts recommended initial evaluation of disease extent and relevant comorbidities or lifestyle factors, along with patient education on disease etiology and scalp/hair care. Management is divided into (1) scalp and (2) face, trunk, or intertriginous involvement. First-line therapy emphasizes anti-inflammatory treatment with topical roflumilast 0.3% foam or corticosteroids. If disease persists, adjunctive antifungals are recommended. For nonscalp areas, alternatives include topicals, calcineurin inhibitors, tapinarof, or ruxolitinib. Recalcitrant or high-impact disease may warrant off-label systemic therapy such as isotretinoin, anti-IL-12/23 biologics, or oral antifungals.

**Conclusions:** This algorithm integrates an updated understanding of SD pathophysiology, prioritizing anti-inflammatory and immune-modulating therapies in management. It provides a practical framework for clinicians to tailor therapy based on disease location, severity, and response to prior treatment. Future studies are needed to validate outcomes and optimize long-term management strategies in diverse patient populations. Further research should clarify mechanisms and refine targeted therapeutic approaches further.

*J Drugs Dermatol.* 2026;25(11):1019-1025. doi:10.36849/JDD.10113

## INTRODUCTION

Seborrheic dermatitis (SD) is a common, chronic inflammatory skin disease that affects approximately 5% of the global population.[1] It is characterized by erythematous patches and plaques with white-yellow greasy scale, generally affecting sebaceous gland-rich areas such as the face, scalp, chest, and upper back.[2] Mild cases may present with isolated flaking; severe cases may involve erythematous, greasy, scaly plaques on the face and trunk. SD is associated with a significant negative impact on patients.[3] In a study evaluating patient-reported level of negative impact of SD, 76% of patients reported some degree of negative impact on their emotional well-being, and 78% reported a significant negative impact on their self-esteem.[3]

SD pathogenesis has historically been thought to be primarily driven by *Malassezia* yeast species, with first-line treatment consisting of antifungal therapy.[4] However, it has become

increasingly understood that an altered immune response is a key step in SD pathogenesis. Rather than a direct causative role of *Malassezia*, recent research suggests that a dysregulated immune environment may allow for increased *Malassezia* growth and activity.[5,6] Recent tape-strip transcriptomic studies of SD skin reveal significant upregulation of T-helper (Th)17 and Th22 pathways, reflecting some similarities in its immune dysregulation with psoriasis.[7] In addition, significant downregulation of key epidermal barrier markers was observed, including CLDN1, CLDN8, FA2H, and ELOVL3, which suggests dysregulation in both barrier integrity and lipid metabolism in the skin.[7] These findings support a hypothesis of immune dysregulation and skin barrier dysfunction underlying inflammation-driven pathogenesis for SD that is distinct from psoriasis and atopic dermatitis. Thus, novel advances in understanding and treating SD are driving a shift in the traditional treatment paradigm, highlighting the need for practical guidance that incorporates emerging innovations.

Historically, the management of SD was based on symptom control and flare reduction, with treatment selection guided by severity and anatomic area. Frequently used topical therapies include topical corticosteroids (TCS), topical antifungals, topical calcineurin inhibitors (TCI), and both prescription and over-the-counter (OTC) and prescription antifungal shampoos.4 A topical phosphodiesterase-4 inhibitor, roflumilast 0.3% foam, was recently approved for the treatment of SD.[4] Systemic agents, such as isotretinoin, oral antifungals, and biologics (anti-IL-12/23 monoclonal antibodies), are also used for severe, refractory cases of SD.[2,4,8,9] In general, most topical and systemic agents used in SD have varying levels of evidence supporting their use. Topical roflumilast is the only agent that has high-quality, proven, and reliable clinical data supporting its efficacy and safety in the treatment of SD.[10,11]

Here, we present an expert-developed practical algorithm for the management of SD in adults and adolescents, informed by recent clinical and translational research to optimize treatment outcomes for patients with SD.

## MATERIALS AND METHODS

The algorithm was developed with input from a group of experts (BU, AA, CGB, EC, AF, HWL, RC) with extensive experience in SD treatment. Initial development was based on the results of a systematic literature review. A draft algorithm was then discussed among the experts and finalized for publication. This manuscript presents the algorithm and considerations that went into its development.

### Systematic Literature Review

Articles addressing SD treatment for adults and adolescents (ages 9 and older) were included from 1 January 2015 to 1 November 2025, including guidelines, meta-analyses, systematic literature reviews, and clinical studies. The literature search was restricted to the past 10 years to inform the treatment algorithm. Review articles were included to represent older seminal literature that would otherwise be outside the 10-year window. The search was conducted on PubMed with Google Scholar as a secondary source. Search terms were as follows: seborrheic dermatitis AND (topical treatment OR antifungals OR corticosteroids OR calcineurin inhibitors OR PDE4 inhibitors) AND (systemic treatment OR JAK inhibitors OR biological therapies OR antifungals OR isotretinoin).

Two reviewers (A Andriessen and H Andriessen) first reviewed titles and abstracts, followed by the full articles. Disagreements were resolved through consensus. Exclusion criteria were pediatric interventions, nonEnglish language, and case reports/series (<20 patients). This search yielded 399 articles, which

**FIGURE 1.** Literature search results.

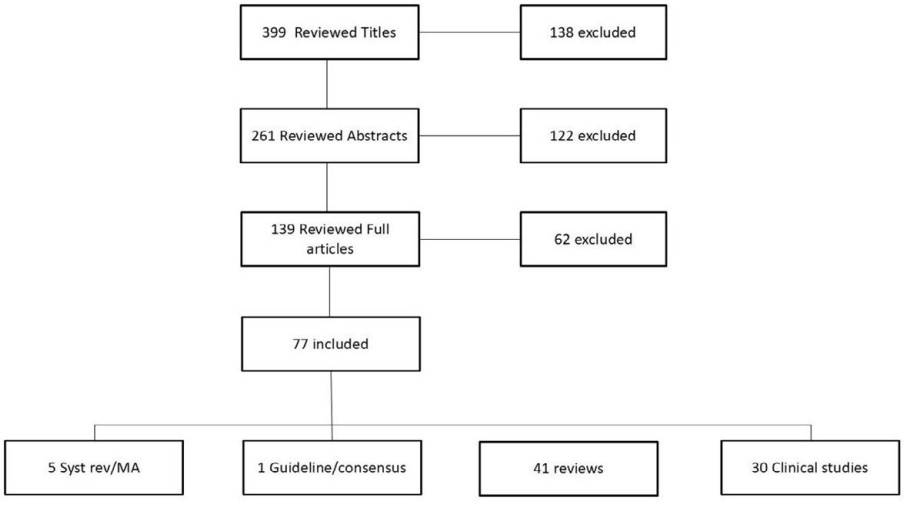


**TABLE 1.**

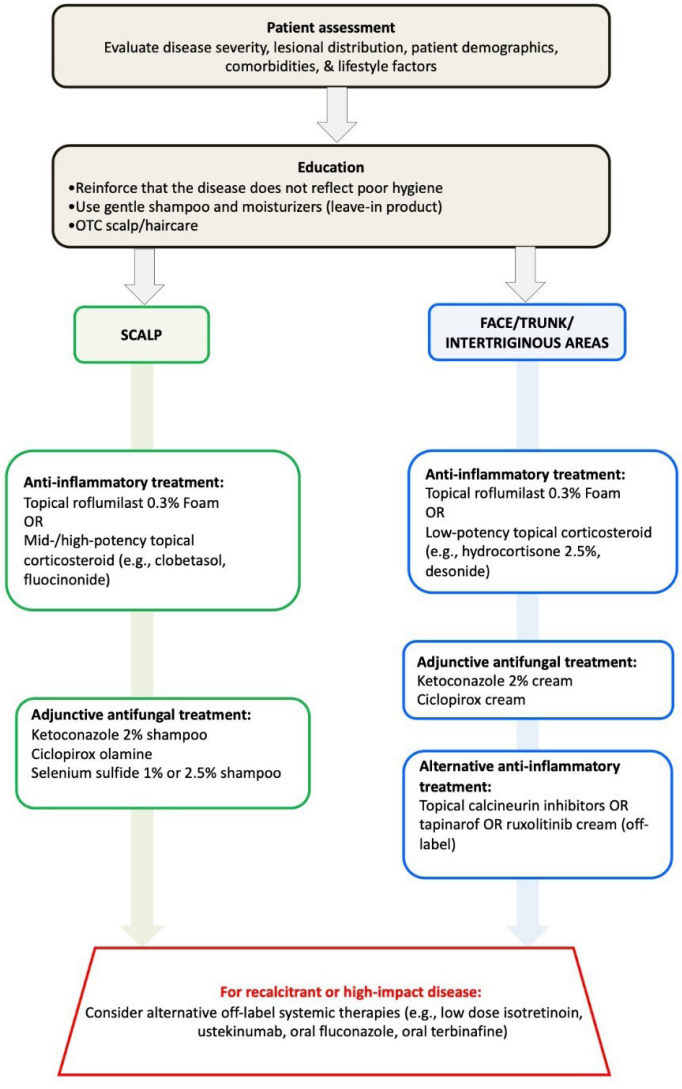
| Grading of Clinical Studies on Skincare[12] | |
|---|---|
| A | Randomized, double-blind clinical trial of high quality |
| B | Randomized clinical trial of lesser quality |
| C | Comparative trial with severe methodologic limitations |
| 1 | Further research is unlikely to change confidence in the effect |
| 2 | Further research is likely to change confidence in the effect |
| 3 | Further research is very likely to change the effect |
| 4 | Any estimate of effect is very uncertain |

were screened; after title evaluation, 138 were excluded, and after abstract evaluation, another 122 were excluded. Of the 139 articles evaluated in full, 62 were excluded. A total of 77 articles were extracted for content analysis, including 5 systematic reviews, 1 clinical guideline, 30 clinical studies, and 41 reviews. (Figure 1). Studies were graded in correspondence with the American Academy of Dermatology evidence-based guideline development process (Table 1).[12]

### Role of Experts

A panel of 6 board-certified dermatologists and one physician assistant convened on December 11, 2025. Following the literature review and the creation of a draft algorithm supported by the literature, the experts participated in a virtual workshop to discuss and adapt the algorithm. The algorithm is based on expert opinions and discussions regarding the challenges of treating adult and adolescent patients with SD, and the need for clear, actionable guidance for clinicians in practice (Figure 2). The algorithm seeks to shift from traditional severity-based disease assessment to recommend therapies based on anatomic location, patient symptoms, and history of treatment resistance. Treatment recommendations are similar for adults and adolescents; however, pediatric disease requires a separate approach and is therefore not covered in this manuscript.

**FIGURE 2.** Algorithm for the treatment of seborrheic dermatitis in adults and adolescents.




Topical treatments
FDA approved: Roflumilast 0.3%, Ketoconazole 2%, Ciclopirox 1%, Selenium disulfide. Not FDA approved (off-label): Miconazole 2%, Betamethasone valerate 0.12%, Clobetasol propionate 0.05%, Hydrocortisone 1%/2.5%, Pimecrolimus 1%, Tacrolimus 0.1%, Ruxolitinib 1.5% Cream, Tapinarof 1% Cream.

**Seborrheic Dermatitis Algorithm for Adults and Adolescents**

The algorithm reflects current evidence and expert consensus on the treatment of SD and begins with patient assessment and education, followed by the provision of treatment options based on anatomic location (Figure 2).

*Patient Assessment*

SD is a clinical diagnosis with clinician-determined severity. Clinicians often classify SD as "mild", "moderate", or "severe", or in clinical studies use an investigator global assessment (IGA) tool; however, these classifications do not consider the anatomic location of affected sites. Instead, the algorithm here proposes patient assessment by affected site, separating scalp SD from face/trunk/intertriginous areas. Patient demographics, such as skin type, must also be considered, as patients with skin of color may also present with hypopigmentation or hyperpigmentation, or as annular, scaly, erythematous patches or polycyclic pink or hypopigmented coalescing rings.[13] Severe, refractory cases of SD may raise clinical suspicion for immunodeficiency or neurologic disease.

SD may also be influenced by environmental conditions and lifestyle/cultural factors.[1] Thus, clinicians should take a thorough patient history as part of their evaluation and assessment. Understanding a patient's life will help inform their understanding of disease. For example, SD has been associated with urban environments, heavy traffic, temperature, ultraviolet (UV) index, stress, and humidity.[2] In addition, the use of added hair extensions and infrequent hair oil application (every 2 weeks) were strongly associated with increased SD incidence in African American females.[14] Further studies have also identified chemical relaxers, pomades, oils, and other scalp treatments were associated with SD flares. Thus, reviewing certain lifestyle factors and comorbidities is important in appropriately guiding patients.

*Patient Education and Supportive Care*

Effective SD management begins with patient education and support. Many patients are unaware of their SD diagnosis and report having difficulty finding information online about the disease. A healthcare provider (HCP) survey study reported that 86% of HCPs felt that "most patients had not heard of SD before their diagnosis".[3] Thus, educating patients about the etiology and course of SD is paramount for SD management.

Part of the discussion should center around hair care, including OTC products and washing habits. There has been a longstanding belief among patients that SD is associated with poor hygiene or poor skin/hair care habits (eg, insufficient hair washing or lack of moisturization on the face). However, evidence has been inconsistent in its support for this. In one study, hair washing every 1 to 2 weeks was not associated with a higher prevalence of SD in girls aged 1 to 15 years.[14] However, a 2-week study of an Asian population reported that a lower frequency of shampooing was associated with increased flakiness, itchiness, and *Malassezia* species burden.[15] More recently, a 3-week study in 60 women of African descent (aged 20–40 years) suggested that SD symptoms may begin as early as 1 week after the last hair wash, leading to recommendations of weekly to biweekly hair washing to prevent SD flares.[16] Thus, patient education should encourage appropriate hygiene regarding the patient's hair type and style without leading to over- or under-washing. The use of gentle shampoos and conditioners without irritating or allergenic ingredients should also be encouraged to further prevent exacerbation. OTC shampoos containing selenium sulfide or zinc pyrithione may help support dandruff treatment through antifungal and anti-inflammatory effects.[17] In a seminal study, Danby et al found that selenium sulfide 2.5% shampoo and ketoconazole 2% shampoo were both equally effective in the treatment of moderate to severe dandruff, making both ingredients appropriate for SD treatment regimens.[17] Additionally, multiple reports have linked decreased lipid levels in the stratum corneum with impaired barrier function and SD.[18,19] Few data exist to make clear recommendations regarding shampoos and body washes for SD. Thus, OTC products containing lipid-replenishing ingredients may prove helpful in SD treatment.

*Topical Treatment*

Topical treatments are a central pillar in SD treatment (Table 2). Topical antifungals have generally been regarded as first-line treatments, alongside TCS and TCI. However, there is a lack of overwhelming/strong data for topical antifungals and TCS.

*Topical roflumilast*

We propose monotherapy topical roflumilast 0.3% foam as a first-line anti-inflammatory, nonsteroidal treatment for SD on the scalp and face/trunk/intertriginous areas, reflecting our shift in understanding of underlying immunological drivers of disease (Figure 2). Roflumilast is a phosphodiesterase 4 inhibitor that decreases the production of proinflammatory cytokines by inhibiting cyclic adenosine monophosphate degradation and is an FDA-approved SD treatment for patients 9 years and older.[20] In the multicentre phase 3 vehicle-controlled trial, roflumilast 0.3% foam was applied once daily as monotherapy in patients aged 9 years or older with SD covering up to 20% of their body surface area (scalp, face, trunk, and/or intertriginous areas). By week 8, roflumilast-treated patients showed significant improvement in their SD, with 79.5% achieving IGA scores of 0 (clear) or 1 (almost clear).[20] Roflumilast also demonstrated a significant reduction in itch as early as week 2 compared to vehicle, with improvement in mean itch scores within 48 hours of the first application, making it an appropriate first-line option for SD management.[20] In addition, long-term efficacy and safety demonstrated a durable response at week 52, with no significant treatment-related safety signals.[10]

**TABLE 2.**

**Topical Treatment for Limited, Localized Seborrheic Dermatitis: Evidence and Side Effects**

| | Treatment | Class | FDA-Approved | Level of Evidence | Conventional Dosing Regimen | Common Potential Side Effects |
|---|---|---|---|---|---|---|
| Topicals | Ketoconazole 2% | Antifungal | Yes | A [1] | 1–2×/day for 2–4 weeks, then 1×/week | Skin dryness, pruritus, stinging, burning, tingling |
| | Ciclopirox 1% | Antifungal | Yes | A [1] | 2×/day for 4 weeks, then 1×/week | Skin dryness, pruritus, stinging, burning, tingling |
| | Miconazole 2% | Antifungal | No | A [1] | 1–2×/day | Skin dryness, pruritus, stinging, burning, tingling |
| | Betamethasone valerate 0.12% | Corticosteroid | No | A [1,2] | For the body; 1–2×/day for up to 3 weeks, then 2×/week | Skin atrophy, telangiectasias, hypertrichosis, perioral dermatitis (all with long-term use) |
| | Clobetasol propionate 0.05% | Corticosteroid | No, off-label | A [1,2] | For the body; 1–2×/day for up to 3 weeks, then 2×/week | Skin atrophy, telangiectasias, hypertrichosis, perioral dermatitis (all with long-term use) |
| | Hydrocortisone 1%/2.5% | Corticosteroid | No | A [1,2] | For the face; 1–2×/day for 7–10 days, then 2×/week | Skin atrophy, telangiectasias, hypertrichosis, perioral dermatitis (all with long-term use) |
| | Pimecrolimus 1% | Calcineurin inhibitor | No, off-label | A [2,3] | 1–2×/day for up to 4 weeks | Application-site burning, erythema, irritation, or itching |
| | Tacrolimus 0.1% | Calcineurin inhibitor | No, off-label | A [2,3] | 1×/day for 4 weeks, then 2×/week | Application-site burning, erythema, irritation, or itching |
| | Roflumilast | Phosphodiesterase 4 inhibitor | Yes | A [4,5] | 1×/day | Nausea, diarrhea, application-site pain |
| | Zinc pyrithione | Antifungal | Yes (combined with ketoconazole) | B [2] | 2–3×/week for 2–4 weeks, then 1×/week or every other week | N/A |
| | Selenium disulfide | Keratolytic, antifungal | Yes | C [1] | 2–3×/week for 2–4 weeks, then 1×/week or every other week | Itching, irritation |
| | Ruxolitinib 1.5% Cream | JAK inhibitor | No, off-label | C [2] | Twice daily for 4-6 weeks | Skin redness or irritation |
| | Tapinarof 1% Cream | Aryl hydrocarbon receptor agonist | No, off-label | C[2] | Once daily | Folliculitis |

**For level of evidence explanation, see Table 1

Roflumilast is formulated as an emollient, fragrance-free, water-based foam without propylene glycol, polyethylene glycol, isopropyl alcohol, or ethanol, making it well tolerated by most patients and associated with a favorable safety profile.[20] Excipients were selected for their low irritant and allergenic potential. This also makes it an appropriate option for diverse skin and hair types, with minimal side effects. Minimal side effects from clinical trial data included nausea (1.6%) and application-site burning and stinging (0.3%).[20]

*Topical Corticosteroids*

If patients experience persistent pruritus or flaking, mid- to high-potency TCS may be used on short-term duration, such as clobetasol propionate 0.05% or fluocinonide 0.05% solution or shampoo on the scalp, to reduce inflammation.[21] For the face/trunk/intertriginous areas, low-potency topical corticosteroids such as hydrocortisone 2.5% or desonide 0.05% may also be considered as adjunctive treatment for recalcitrant areas. Use of TCS is limited by its adverse event profile, including skin atrophy, acne, striae, hypopigmentation, or rarely systemic absorption leading to suppression of the hypothalamic-pituitary-adrenal axis. These side effects may lead many patients to be "steroid-phobic," leading to poor treatment compliance and under-treatment.[22]

*Topical calcineurin inhibitors*

TCI, such as tacrolimus or pimecrolimus, may also be considered as a nonsteroidal, anti-inflammatory alternative. In a systematic review of 4 randomized controlled trials, topical

**TABLE 3.**

**Systemic Treatment for Limited, Localized Seborrheic Dermatitis, Evidence and Side Effects**

| | Treatment | Class | FDA-Approved | Level of Evidence | Conventional Dosing Regimen | Common Potential Side Effects |
|---|---|---|---|---|---|---|
| Systemics | Itraconazole | Antifungal | No, off-label | A [1] | 200 mg/day for7days, then 200 mg weekly for 2–11 months | Nausea, headache, drug-drug interactions |
| | Fluconazole | Antifungal | No, off-label | A [1] | 200 mg/weekly for 4 weeks, OR 300 mg/ week for 2 weeks | Elevated liver function tests, nausea |
| | Terbinafine | Antifungal | No, off-label | A [3] | 250 mg/day for 4–6 weeks | Taste disorders, tachycardia, insomnia, gastrointestinal symptoms, migraines, rash; rarely liver injury |
| | Isotretinoin | Retinoid | No, off-label | A [4] | 10–20 mg/day or every other day for 2–6 months | Cheilitis, nose bleeds, skin fragility, skin dryness, myalgias |
| | Ustekinumab | Monoclonal Antibody | No, off-label | C [4] | 45 mg or 90 mg subcutaneously at week 0, 4, ~every 12 weeks thereafter | URIs |

**For level of evidence explanation, see Table 2

pimecrolimus was found to be comparable in efficacy to topical corticosteroids and antifungals in reducing erythema, pruritus, and scaling in patients with SD.[23] These nonsteroidal options are appropriate for use on the face/trunk/intertriginous areas if needed for refractory SD treatment or in long-term therapy. Other nonsteroidal topical treatments have been shown to be effective for SD. An open-label trial of the topical JAK inhibitor ruxolitinib 1.5% cream demonstrated efficacy in treating SD by targeting JAK1 and JAK2, thereby reducing pro-inflammatory cytokine signaling and improving inflammatory skin disease.[24, 25] Similarly, topical tapinarof 1% cream, an aryl-hydrocarbon receptor agonist, has demonstrated efficacy in a 4-patient case series of patients with moderate-to-severe SD, with clinical improvement observed within 1 week of treatment (Table 2).[26]

*Azoles*

Antifungals may help reduce *Malassezia spp.* burden, potentially further exacerbating inputs into the proinflammatory state in SD.[18]

Topical azoles such as ketoconazole 2% shampoo, ciclopirox olamine, and selenium sulfide 1% or 2.5% shampoo may be used as adjunctive treatment for those with resistant forms of SD across different body areas (Figure 2). However, azole resistance has become an increasingly significant global concern.[27] Evidence shows that dermatophyte resistance to azoles is increasing, with rates reported as high as 19%.[28] This is largely driven by repeated exposure to topical azole therapies and inappropriate use of over-the-counter antifungals and steroid combinations.[27-29] Ketoconazole 2% shampoo used once weekly has been shown to be effective in preventing SD flares, and when combined with clobetasol propionate 0.05% shampoo, leads to greater efficacy in SD clearance.[30] Ketoconazole 2% shampoo (twice weekly application) has been shown to be superior to zinc pyrithione and 2.5% selenium sulfide in scalp SD.[31,32] However, more recent studies demonstrate earlier symptom relief with selenium sulfide than ketoconazole.[33] For the facial and trunk SD, multiple studies have demonstrated that 2% ketoconazole cream was superior to vehicle or equivalent in efficacy to 1% hydrocortisone cream.[34] Antifungal treatment may be helpful in skin of color populations, where SD was found to be amongst the top 5 most common dermatological conditions in African Americans compared to White, Hispanic, and Asian patients.[6]

Given emerging evidence supporting SD as an immune-driven disease, the use of nonsteroidal agents such as roflumilast may be a more appropriate option. Overall, treatment of SD with effective anti-inflammatory agents may reduce the necessity and frequency of antifungal application. Lessening antifungal use, such as ketoconazole, will improve antifungal stewardship and may reduce the development of azole resistance in the future.[27]

*Systemic Treatment/Advanced Treatment*

Severe, treatment-refractory SD with high BSA involvement may be treated with systemic agents (Table 3). Oral, low-dose (<0.5 mg/kg/day) isotretinoin has demonstrated efficacy in the treatment of SD, with patients reporting a significant reduction in erythema, scaling, and sebum production by 3 months of treatment.[35,36] Further studies compared 10 mg to 20 mg isotretinoin and reported no significant difference in reducing SD symptoms.[37] Isotretinoin reduces sebum production, thereby indirectly targeting *Malassezia* colonization by reducing the

availability of its lipid substrate, while also conferring anti-inflammatory effects.

IL-12/23 targeting with ustekinumab has some evidence supporting its effectiveness in treating SD, with clearance after only a few doses and lasting remission.[9]

Oral antifungals have also been recommended for severe SD.[2] Terbinafine (250 mg/day for 4 to 6 weeks) has demonstrated efficacy in some cases, while oral fluconazole has shown more variable results.[2,38] Although these medications may benefit certain patients, current evidence suggests that SD management should move away from routine use of oral antifungals. Both terbinafine and fluconazole carry the risk of liver toxicity with long-term use and significant drug-drug interactions. In addition, their overuse may contribute to rising antifungal resistance while failing to address the primary inflammatory driver of SD.

## CONCLUSION

SD is a common, chronic inflammatory skin disease characterized by immune dysregulation and skin barrier dysfunction leading to increased sebum production and commensal *Malassezia* growth. Clinical presentation may range from mild scalp dandruff to severe erythematous, greasy, scaly plaques on the scalp, face, and trunk, representing a wide SD spectrum. Here, we present a practical algorithm that integrates novel understanding of SD pathogenesis as an inflammatory condition with Th17/Th22 skewing, thereby requiring immune-modulatory treatments. The practical algorithm reflects a shift from antifungal to anti-inflammatory and immune-modulatory treatments. The length of treatment, adjunctive treatment, and maintenance regimens will be important to consider for each patient. Future studies and discussions will be necessary to evaluate these long-term regimens and to delineate SD treatment for pediatric patients under 9 years of age.

## DISCLOSURES

The research for this work was supported by an educational grant from Arcutis Biotherapeutics©. All authors contributed to the development of the manuscript, reviewed, and agreed with its content and submission. BU is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Bristol Myers Squibb, Incyte, Leo Pharma, Rapt Therapeutics, Pfizer, and Sanofi. He is also a consultant for AbbVie, Arcutis Biotherapeutics, Apogee Therapeutics, Bristol Myers Squibb, Botanix Pharmaceuticals, Castle Biosciences, Ebla Holdco, Fresenius Kabi, Galderma, Incyte, J&J, Leo Pharma, Lilly, Nektar Therapeutics, Pfizer, Primus Pharmaceuticals, Sanofi, Sun Pharma, UCB, Veradermics, VRG Therapeutics. All other authors have no conflicts of interest.

## REFERENCES

1. Polaskey MT, et al. The global prevalence of seborrheic dermatitis: a systematic review and meta-analysis. *JAMA Dermatol.* 2024;160(8):846-855.
2. Turchin I, et al. Current understanding of seborrheic dermatitis: epidemiology, burden of disease, and pathophysiology. *J Cutan Med Surg.* 2025;29(4_suppl):5S-15S.
3. Chovatiya R, et al. Patient and healthcare provider perspectives on the pathway to diagnosis of seborrheic dermatitis in the United States. *Adv Ther.* 2024;41(12):4433-4445.
4. Gupta AK, Richardson M, Paquet M. Systematic review of oral treatments for seborrheic dermatitis. *J Eur Acad Dermatol Venereol.* 2014;28(1):16-26.
5. Piacentini F, et al. Seborrheic dermatitis: exploring the complex interplay with Malassezia. *Int J Mol Sci.* 2025;26(6).
6. Jackson JM, et al. Unmet needs for patients with seborrheic dermatitis. *J Am Acad Dermatol.* 2024;90(3):597-604.
7. Ungar B, et al. Tape-strip profiling identifies unique immune and lipid dysregulation in patients with seborrheic dermatitis. *J Am Acad Dermatol.* 2025;92(6):1277-1287.
8. Vidal SI, Menta N, Green L. Child and adult seborrheic dermatitis: a narrative review of the current treatment landscape. *Dermatol Ther (Heidelb).* 2025;15(3):599-613.
9. Ghalili S, et al. IL-12/23-targeting in seborrheic dermatitis patients leads to long-lasting response. *Arch Dermatol Res.* 2023;315(10):2937-2940.
10. Alexis AF, et al. Long-term safety and efficacy of roflumilast foam 0.3% in patients with seborrheic dermatitis: a phase II, open-label trial of up to 52 weeks. *Am J Clin Dermatol.* 2026;27(1):189-198.
11. Zirwas MJ, et al. Efficacy of roflumilast foam, 0.3%, in patients with seborrheic dermatitis: a double-blind, vehicle-controlled phase 2a randomized clinical trial. *JAMA Dermatol.* 2023;159(6):613-620.
12. Smith Begolka W, Elston DM, Beutner KR. American Academy of Dermatology evidence-based guideline development process: responding to new challenges and establishing transparency. *J Am Acad Dermatol.* 2011;64(6):e105-e112.
13. Elgash M, et al. Seborrheic dermatitis in skin of color: clinical considerations. *J Drugs Dermatol.* 2019;18(1):24-27.
14. Rucker Wright D, et al. Hair care practices and their association with scalp and hair disorders in African American girls. *J Am Acad Dermatol.* 2011;64(2):253-262.
15. Punyani S, et al. The impact of shampoo wash frequency on scalp and hair conditions. *Skin Appendage Disord.* 2021;7(3):183-193.
16. Fajuyigbe D, et al. Weekly hair washing: the recommended solution for women with afro-textured hair to alleviate dandruff and scalp discomfort. *J Dermatol.* 2024;51(4):518-525.
17. Borda LJ, Perper M, Keri JE. Treatment of seborrheic dermatitis: a comprehensive review. *J Dermatolog Treat.* 2019;30(2):158-169.
18. Hordinsky M, et al. Etiology, treatment challenges, and the role of scalp and haircare in managing dandruff. *J Drugs Dermatol.* 2025;24(2):s8-s14.
19. Bitton A, et al. A clinical evaluation of scalp barrier function, ceramide levels, and microbiome in diverse dandruff patients. *J Drugs Dermatol.* 2025;24(3):32731s3-32731s14.
20. Blauvelt A, et al. Roflumilast foam 0.3% for adolescent and adult patients with seborrheic dermatitis: a randomized, double-blinded, vehicle-controlled, phase 3 trial. *J Am Acad Dermatol.* 2024;90(5):986-993.
21. Reygagne P, et al. Clobetasol propionate shampoo 0.05% in the treatment of seborrheic dermatitis of the scalp: results of a pilot study. *Cutis.* 2007;79(5):397-403.
22. Contento M, Cline A, Russo M. Steroid phobia: a review of prevalence, risk factors, and interventions. *Am J Clin Dermatol.* 2021;22(6):837-851.
23. Ang-Tiu CU, Meghrajani CF, Maano CC. Pimecrolimus 1% cream for the treatment of seborrheic dermatitis: a systematic review of randomized controlled trials. *Expert Rev Clin Pharmacol.* 2012;5(1):91-97.
24. Pope E, Kowalski E, Tausk F. Topical ruxolitinib in the treatment of refractory facial seborrheic dermatitis. *JAAD Case Rep.* 2022;24:59-60.
25. Manson M, et al. 0472 Topical ruxolitinib 1.5% cream improves immune and barrier dysregulation in patients with moderate-to-severe seborrheic dermatitis. *J Invest Dermatol.* 2025;145(8):S81.
26. Issa NT, Pomaville L. Real-world use of tapinarof cream 1% once daily in patients with seborrheic dermatitis: a case series. *J Clin Aesthet Dermatol.* 2025;18(1):24-28.
27. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. *Lancet Infect Dis.* 2017;17(12):e383-e392.
28. Badiee P, et al. Comparison of in vitro activities of newer triazoles and classic antifungal agents against dermatophyte species isolated from Iranian University Hospitals: a multi-central study. *Ann Clin Microbiol Antimicrob.* 2023;22(1):15.
29. Paiva Macedo J, Dias VC. Antifungal resistance: why are we losing this battle? *Future Microbiol.* 2024;19(11):1027-1040.
30. Ortonne JP, et al. Efficacious and safe management of moderate to severe scalp seborrhoeic dermatitis using clobetasol propionate shampoo 0.05% *combined with ketoconazole shampoo 2%: a randomized, controlled study. Br J Dermatol.* 2011;165(1):171-176.
31. Pierard-Franchimont C, et al. A multicenter randomized trial of ketoconazole 2% and zinc pyrithione 1% shampoos in severe dandruff and seborrheic dermatitis. *Skin Pharmacol Appl Skin Physiol.* 2002;15(6):434-441.
32. Danby FW, et al. A randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo in the treatment of moderate to severe dandruff. *J Am Acad Dermatol.* 1993;29(6):1008-1012.
33. Barbosa V, et al. A comparative randomized clinical study assessing the efficacy of a 1% selenium disulfide-based shampoo versus 2% ketoconazole shampoo in subjects with moderate to severe scalp seborrheic dermatitis. *Skin Appendage Disord.* 2024;10(6):497-504.
34. Choi FD, Juhasz MLW, Atanaskova Mesinkovska N. Topical ketoconazole: a systematic review of current dermatological applications and future developments. *J Dermatolog Treat.* 2019;30(8):760-771.
35. Alsayoud FM, et al. Efficacy and safety of isotretinoin for moderate-to-severe seborrheic [illegible]s. *Clin Cosmet Investig* [illegible] for moderate to severe

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Peptides for Hair Growth and Treatment of Hair Loss and Alopecia: A Systematic Review

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## ABSTRACT

**Background:** Patients desire products that will result in hair growth and treatments to address concerns of hair loss in alopecia. Peptide-based formulations represent established, promising, and safe therapeutics that target hair growth pathways.

**Methods:** On November 3, 2025, PubMed, Embase, and the Cochrane Library were searched per PRISMA guidelines for English-language clinical trials assessing peptide-containing therapies for hair loss in human subjects.

**Results:** Of the 981 studies identified, 14 met the inclusion criteria. Grade of recommendation: B for formulations with acetyl tetrapeptide-3, biotinoyl tripeptide-1, glycyl-histidyl-lysine peptide, and penta-peptide Gly-Pro-Ile-Gly-Ser. Grade of recommendation: C for QR678 and QR678 Neo®.

**Conclusion:** Clinical data support peptide-based formulations, particularly combinations containing acetyl tetrapeptide-3, biotinoyl tripeptide-1, and glycyl-histidyl-lysine peptide as effective, well-tolerated alternatives to conventional hair-growth therapies.

*J Drugs Dermatol.* 2026;25(11):1026-1032. doi:10.36849/JDD.9736

## INTRODUCTION

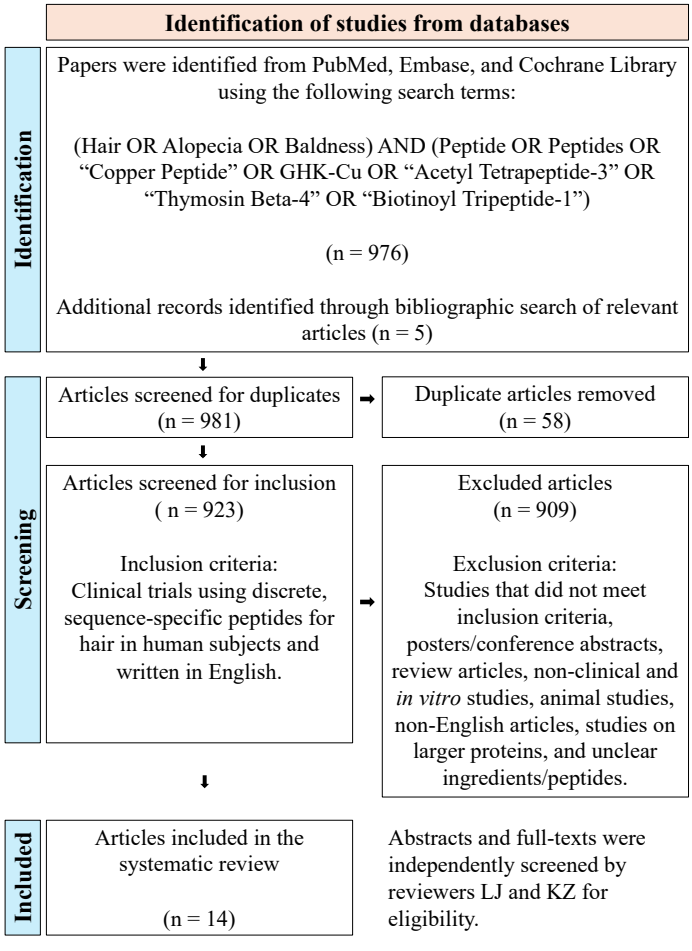
Many patients seek interventions to achieve thicker, fuller hair for aesthetic enhancement. Hair loss is a multifactorial condition impacting the majority of men and women worldwide during their lifetimes.[1] Hair loss encompasses a spectrum of etiologies, including androgenetic alopecia (AGA), telogen effluvium, alopecia areata, and central centrifugal cicatricial alopecia.[2] Beyond physical concerns, hair loss poses a psychosocial burden, associated with poor self-esteem, stress, anxiety, depression, and impaired quality of life.[3,4]

Hair loss is influenced by intrinsic and extrinsic factors. Intrinsic contributors include hormone imbalance, genetic predisposition, autoimmune processes, and alterations in follicular cycling.[2] The androgen dihydrotestosterone (DHT), produced through 5α-reductase activity, is particularly implicated in follicular miniaturization and shortened anagen duration.[5] Psychological stressors, including anxiety and depression, may precipitate hair loss.[5,6] Extrinsic factors, including lifestyle patterns, pollution, and ultraviolet radiation, increase oxidative stress, inducing hair follicle apoptosis and atrophy.[6]

Current treatments aim to enhance aesthetic hair density and quality and prevent follicular loss. First-line therapies, minoxidil and finasteride, are effective in early disease, but their effects diminish over time and can result in adverse effects (AEs).[7] Oral minoxidil can cause tachycardia, headaches, and hypertrichosis, while finasteride has been linked to permanent sexual dysfunction and depression.[8,9] In advanced stages, patients often pursue procedural interventions, including intradermal injections of platelet-rich plasma (PRP) or follicular unit transplantation.[10,11]

Peptides have recently emerged as promising bioactive molecules in hair restoration therapy and aesthetic enhancement. Peptides are chains of 2 to 50 amino acids that can modulate follicular biology through targeted mechanisms.[12] Research suggests that peptides can strengthen extracellular matrix (ECM) integrity, stimulate dermal papilla activity, improve microcirculation, and prolong the anagen (growth) phase of the hair cycle.[12,13] Clinical data support these mechanisms, demonstrating significant improvements in hair density, thickness, and investigator-assessed outcomes.[14] Herein, we summarize the safety and efficacy of peptide-based formulations for hair growth, elucidate underlying mechanisms of action, and identify gaps to guide future trial design and optimize clinical integration.

**FIGURE 1.** PRISMA flow diagram for the systematic review of peptides for the treatment of hair loss.




## MATERIALS AND METHODS

A systematic search of PubMed, Cochrane Library, and Embase databases was performed on November 3, 2025, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines (Figure 1).

## RESULTS

Our systematic search yielded 981 papers. After title, abstract, and full-text screening, 14 clinical trials met the inclusion criteria. The studies evaluated formulations with the following peptides: biotinoyl tripeptide-1 (3), QR678 and QR678 Neo® (6), acetyl tetrapeptide-3 (2), glycyl-histidyl-lysine peptide (2), and penta-peptide Gly-Pro-Ile-Gly-Ser (1). The peptide formulations are organized alphabetically by grade of recommendation, as defined inTable 1. Study characteristics are summarized inTable 2.

**TABLE 1.**

| Level of Evidence and Grades of Recommendation per Oxford Center for Evidence-based Medicine[26] |
|---|
| Level of Evidence |
| 1a. Systematic review of RCTs |
| 1b. Individual RCT |
| 2a. Systematic review of cohort studies |
| 2b. Individual cohort study (including low-quality RCT) |
| 3a. Systematic review of case-control studies |
| 3b. Individual case-control study |
| 4. Case series |
| 5. Case reports, expert opinion, bench research |
| Grades of Recommendation |
| A. Consistent level 1 studies |
| B. Consistent level 2 or 3 studies or extrapolations from level 1 studies |
| C. Level 4 studies or extrapolations from level 2 or 3 studies |
| D. Level 5 evidence or troubling inconsistent or inconclusive studies of any level |

RCT, randomize controlled trial

**TABLE 2.**

**Baseline Demographic Characteristics of the Celecoxib, Sirolimus, and Acitretin Cohorts After Propensity Score Matching (PSM)**

| Author (Year) | Main Treatment Ingredients | Subjects | Intervention | Treatment-Duration | Clinical Findings | Adverse Effects (related to product) |
|---|---|---|---|---|---|---|
| **Acetyl tetrapeptide-3** | | | | | | |
| Loing (2013)[15] | Acetyl tetrapeptide-3, biochanin A, and trifolium pratense flower extract | 30 participants with AGA (age not reported) | 20 drops of lotion with 5% product (300 ppm acetyl tretrapeptide-3) daily | 120 days | Strong increase in anagen hair, decrease in telogen hair, and increase in anagen/telogen ratio compared to placebo | None |
| Lueangarun (2020)[13] | Acetyl tetrapeptide-3, biochanin A, and ginseng extracts | 32 participants with AGA (mean age 41.3) | Topical 1mL of herbal extract twice daily to scalp<br><br>3% minoxidil | 168 days | Herbal extract formulation and 3% minoxidil demonstrated similar efficacy, with no significant difference between groups<br><br>Significant improvement in terminal hair count and hair mass index in both groups | Scalp eczema with 3% minoxidil (n=1) |
| **Biotinoyl tripeptide-1** | | | | | | |
| Wu (2025)[6] | Biotinoyl tripeptide-1 and *Phyllanthus emblica* | 40 participants with hair loss (age range, 25–55) | One spray of 0.1g peptide formulation to the right scalp twice daily<br><br>Left scalp placebo | 90 days | Significantly improved hair mass, density, and vellus hair in men<br><br>Significantly increased vellus hair and total hair density in women | None |
| Voiculescu (2025)[14] | Biotinoyl tripeptide-1, oleanolic acid, and apigenin (Minoxicapil) | 48 participants with AGA (age range, 19-79) | 10–12 sprays (0.2 mL per spray) of peptide formulation<br><br>Combination: Spray and antioxidant oral formulation | 90 days | Significantly improved hair density, hair shaft thickness, empty follicles, and anagen to telogen ratio<br><br>Combination group had a significantly greater increase in total and anagen hair count than that of spray alone | Dryness (n=5), itching (n=5), dandruff (n=2), increased sebum (n=4), and gastrointestinal effects (n=3) |
| Garre (2018)[17] | Biotinoyl tripeptide-1, oleanolic acid, apigenin, diaminopyrimidine oxide, adenosine, biotin and ginkgo biloba extract | 56 participants with AGA or telogen effluvium (age range, 25–50) | Topical formulation once daily | 180 days | Significantly increased number of anagen and total hair count<br><br>39% developed clinically significant scalp coverage | None |
| **Glycyl-histidyl-lysine peptide** | | | | | | |
| Lee (2016)[12] | Glycyl-histidyl-lysine (GHK) peptide and 5-aminolevulinic acid (5-ALA) (ALAVAX complex) | 45 men with AGA (age range, 25–60) | 100 mg/mL spray ALAVAX daily<br><br>50 mg/mL spray ALAVAX daily<br><br>Placebo | 180 days | Significantly increased hair count for 100 mg/mL ALAVAX and 50 mg/mL ALAVAX groups, unlike the placebo<br><br>Significant difference in the ratio of change in hair count between 50 mg/mL ALAVAX and placebo<br><br>No significant difference in hair thickness and length among the treatment groups | None |
| Rinaldi (2019)[18] | Copper tripeptide-1 (GHK-Cu), octapeptide-2, oligopeptide-20, and acetyl decapeptide-3 (TR-M-PRP plus) | 60 participants with AGA (age range, 18–60) | Topical 15 mL peptide lotion twice weekly<br><br>Placebo | 90 days | Significantly improved SALT scores from baseline, greater than placebo | None |
| **Penta-peptide Gly-Pro-Ile-Gly-Ser** | | | | | | |
| Iwabuchi (2016)[20] | Penta-peptide Gly-Pro-Ile-Gly-Ser (GPIGS) | 22 Japanese men with AGA (age range, 28-49) | Topical 3 mg penta-peptide twice daily<br><br>Placebo | 120 days | Significantly less vellus hair, more thick hair, and less visual hair loss than placebo | None |

**TABLE 2. (CONTINUED)**

| Baseline Demographic Characteristics of the Celecoxib, Sirolimus, and Acitretin Cohorts After Propensity Score Matching (PSM) | | | | | | |
|---|---|---|---|---|---|---|
| **Author (Year)** | **Main Treatment ngredients** | **Subjects** | **Intervention** | **Treatment-Duration** | **Clinical Findings** | **Adverse Effects (related to product)** |
| **QR678 and QR678 Neo®** | | | | | | |
| Kapoor (2018)[23] | Copper tripeptide-1, thymosin β4, vascular endothelial growth factor (VEGF; human oligopeptide-11), fibroblast growth factor (FGF; human oligopeptide-3), insulin-like growth factor-1 (IGF-1; human oligopeptide-2), and keratinocyte growth factor (KGF) (QR678®) | 1,000 participants with AGA (age range, 20–60) | 1.5 mL scalp injections every 3 weeks for 8 sessions | 147 days | Significantly increased total hair count after 1 year<br><br>Significantly decreased hair fall in 83% of participants<br><br>Most patients had improved number of vellus and terminal hairs and shaft diameter | 15% of patients experienced scalp itching |
| Kapoor (2020)[22] | QR678® (see above) | 20 women with PCOS and female pattern alopecia (age range, 25-50) | 1.5 mL scalp injections every 3 weeks for 8 sessions | 147 days | Significantly improved vellus and terminal hair count and hair shaft diameter<br><br>Improved GPA score | None |
| Kapoor (2020)[11] | QR678® (see above) | 50 men with AGA (age range, 25–50) | 1.5 mL QR678 scalp injections every 3 weeks for 8 sessions<br><br>Injections with PRP | 147 days | 100% reduction in hair fall out over 1 year, unlike PRP.<br><br>Significantly improved hair density, terminal hair density, vellus hair density, and shaft diameter compared to PRP | QR678 group: painful administration (n=7) PRP group: painful administration (n=22), itchy scalp, and light-headedness |
| Clinic (2022)[24] | Copper tripeptide-1, sh-polypeptide-9, sh-oligopeptide-2, sh-polypeptide-3, sh-polypeptide-1, and sh-oligopeptide-4 (QR678 Neo®) | 2428 participants with AGA (age range, 18-65) | 1 mL scalp injections every 3 weeks for 8 sessions | 147 days | Positive hair pull test in only 12% of patients<br><br>Improvement in GPA score<br><br>Significant improvement in vellus and terminal hair count and average hair shaft diameter | Itching (1.85%) and painful administration (1.2%) |
| Shome (2022)[25] | QR678 Neo® (see above) | 20 women with telogen effluvium after Covid-19 (mean age 35) | 1.5 mL scalp injections every 4 weeks for 8 sessions | 196 days | 87% participants reached a negative pull test<br><br>Significantly improved hair count<br><br>Substantial improvement In GPA scores<br><br>Patient self-assessment resulted in high satisfaction scores for hair growth, hair appearance, and reduction in scalp visibility | Itchy scalp (n=2) and painful administration (n=1) |
| Gold (2025)[7] | QR678 Neo® (see above) | 112 males with AGA (age range, 25–50) | Group A: Hair transplant with QR678 Neo®: (1) 1mL intradermal injections, (2) follicular units diluted in QR678 Neo® solution, (3) post-transplant administration<br><br>Group B: Traditional hair transplant | Based on alopecia severity | Significantly better hair regrowth, density, and shaft diameter than traditional hair transplant | None |

## DISCUSSION

**Acetyl Tetrapeptide-3**

The efficacy of acetyl tetrapeptide-3-based formulations was evaluated in two RCTs (Table 2). A 4-month RCT involving 30 participants assessed the efficacy of acetyl tetrapeptide-3 combined with biochanin A and flower extract. The combination increased anagen hair (+13%), decreased telogen hair (-29%), and improved anagen/telogen ratio (+46%) compared with placebo (anagen, -2%; telogen, +23%; anagen/telogen ratio, -33%). No adverse events (AEs) were reported. Proposed mechanisms include enhanced ECM synthesis, 5α-reductase inhibition, and attenuation of inflammation.[15]

The second RCT compared an herbal extract combination containing acetyl tetrapeptide-3, biochanin A, and ginseng extracts with 3% minoxidil over 24 weeks. Both groups demonstrated significant improvements in terminal hair count (8.3%, $P$=0.009; 8.7%, $P$=0.002, respectively) and hair mass index (13.8%, $P$=0.008; 31.5%, $P$=0.026), with no significant difference between groups. One patient using 3% minoxidil developed eczema.[13] By increasing hydroxyproline, type III collagen, and laminin, the peptide formulation enhances the dermal papilla ECM, leading to increased follicle size and anchorage.[15] In vitro data suggest that biochanin A and acetyl tetrapeptide-3 may also reduce proinflammatory cytokine expression and improve dermal papilla cell proliferation.[15]

**Grade of recommendation:** B for acetyl tetrapeptide-3 for the treatment of hair loss based on 2 level 2b studies (Table 1).

**Biotinoyl tripeptide-1**

The efficacy of biotinoyl tripeptide-1 formulations was evaluated in three studies (Table 2). In a 90-day open-label, split-scalp study, 40 participants applied 0.1 g biotinoyl tripeptide-1 and fruit extract formulation (Biosea Revive serum or BRS) to their right scalp twice daily. Treatment with BRS significantly improved hair mass, density, and vellus hair count in men ($P$<0.05), and improved vellus hair and total hair density in women ($P$ <0.05). In vitro, BRS enhanced dermal papilla cell proliferation compared with the control ($P$<0.05), similar to minoxidil. BRS also inhibited 5α-reductase expression ($P$<0.05) and decreased reactive oxygen activity, further resembling minoxidil's effects. Transepidermal water loss decreased significantly in the female BRS group, indicating improved scalp barrier integrity. No AEs or lab abnormalities were reported, supporting the long-term safety and efficacy of BRS in both genders.[6]

BRS promotes hair growth through a multi-mechanistic approach. Biotinoyl tripeptide-1 inhibits 5α-reductase, thus decreasing DHT and its downstream effects of follicle atrophy and impaired hair growth.[6] *Phyllanthus emblica* fruit extract enhances dermal papilla proliferation, prolongs the anagen phase, and prevents hair follicle atrophy from ROS damage.[16]

Another open-label, 3-month study investigated a topical spray containing biotinoyl tripeptide-1, oleanolic acid, and apigenin (Minoxicapil), alone or in combination with oral capsules, in 48 participants with AGA. The overall study population demonstrated significant improvements in hair density, hair shaft thickness, empty follicles, and anagen-to-telogen ratio ($P$<0.05). Combination therapy demonstrated a greater increase in total and anagen hair count compared to the topical spray group ($P$<0.05). Minor AEs were reported (n=19).[14]

A third open-label study involving 56 participants applied a combination formulation with biotinoyl tripeptide-1, oleanolic acid, apigenin, diaminopyrimidine oxide, adenosine, biotin, and ginkgo biloba extract. Significant increases were observed in anagen hair count and total hair count (median increases of 5% and 9%, respectively; $P$<0.05). The formulation significantly improved hair thickness, similar to Minoxicapil. Based on a dermatologist's clinical assessment, 39% of participants achieved clinically significant scalp coverage. No AEs were reported.[17]

These findings suggest that trichologic improvement is mediated by both hormonal and vascular modulation. Oleanolic acid and biotinyl tripeptide-1 inhibit 5α-reductase, reducing DHT-driven follicular miniaturization.[14] Apigenin enhances perifollicular angiogenesis, vasodilation, and microcirculation through VEGF and nitric oxide synthesis.[17] Oleanolic acid-mediated activation of Wnt/β-catenin signaling promotes follicular stem cell activation and prolongs the anagen phase.[14]

**Grade of recommendation:** B for the biotinoyl tripeptide-1 formulations for hair growth based on 1 level 2b study and 2 level 4 studies.

**Glycyl-Histidyl-Lysine Peptide**

One RCT involving 45 men with male-patterned hair loss evaluated ALAVAX, a combination therapy containing 5-aminolevulinic acid (5-ALA) and glycyl-histidyl-lysine (GHK) peptide. Treatment with ALAVAX at 50 mg/mL and 100 mg/mL resulted in significant increases in hair count (71.5 and 52.6, respectively; $P$<0.05) compared with placebo. The ratio of change in hair count was significantly greater in the 50mg/mL ALAVAX group than in the placebo group (2.38 and 1.21, respectively; $P$<0.05). No significant differences in hair thickness or length were observed among the treatment groups.[12] These results are supported by a 3-month RCT revealing that a copper tripeptide-1 (GHK-Cu) formulation TR-M-PRP significantly improved Severity of Alopecia Tool scores in participants with alopecia areata.[18] No AEs were reported in either study. GHK-Cu supports hair growth by stimulating angiogenesis, ECM production, and stem cells to promote follicle growth.[18] Emerging data suggest that the copper-free GHK peptide exerts similar effects.[19]

**Grade of recommendation:** B for copper tripeptide-1 formulations for the treatment of hair loss based on 2 level 2b studies (Table 1).

**Penta-Peptide Gly-Pro-Ile-Gly-Ser**

In a 4-month study of 22 men with AGA, topical GPIGS (6 mg/day) resulted in significantly less vellus hair ($P$=0.029), thicker hair ($P$=0.006), and less visible hair loss ($P$=0.020) compared with placebo. No treatment-related AEs were observed.[20] Prior research demonstrated that GPIGS increased murine hair keratinocyte proliferation.[21] The effects of GPIGS are thought to be mediated by stimulation of hair-follicle keratinocytes and hair shaft growth, potentially by lengthening the anagen phase of hair growth.[20]

**Grade of recommendation:** B for penta-peptide Gly-Pro-Ile-Gly-Ser for the treatment of hair loss based on 1 level 2b study (Table 1).

**QR678 and QR678 Neo®**

QR678 and QR678 Neo®, containing copper tripeptide-1 and growth factor formulations, were investigated in 6 clinical trials (Table 2). QR678 Neo® is a plant-derived polypeptide formulation that replicates the biological activity of growth factors found in QR678.[22]

In an open-label, pilot study with 1,000 participants, 8 sessions of 1.5 mL QR678 scalp injections over 21 weeks significantly increased total hair count after one year ($P$=0.002), and 83% of participants exhibited significantly reduced hair shedding on the hair pull test. Improvements were observed in vellus and terminal hair counts and shaft diameter. Scalp itching was reported by 15% of patients.[23]

In a prospective study of 20 women with female pattern alopecia from polycystic ovary syndrome, QR678 significantly increased vellus and terminal hair counts and hair shaft diameter ($P$<0.05). Over one year, participants experienced profound improvement in Global Photographic Assessment (GPA) scores (mean=8 out of a 10-point scale), with no AEs.[22]

QR678 therapy was compared to PRP in a randomized, single-blind study in 50 men with AGA. Over 1 year, hair-pull tests revealed that QR678 led to a 100% reduction in hair fall. The QR678 group demonstrated significantly improved hair density, terminal hair density, vellus hair density, and shaft diameter compared with the PRP group ($P$<0.05), with fewer AEs. The QR678 and QR678 Neo formulations have equivalent efficacy; thus, these results apply to both formulations.[11]

An open-label, multi-ethnicity phase IV trial evaluating QR678 Neo® in 2428 participants found 12% had a positive hair pull test after treatment, and the mean GPA score increased from 6 to 8. The vellus and terminal hair counts and average hair shaft diameter increased significantly ($P$<0.05). Itching (1.85%) and injection discomfort (1.2%) were the most common AEs.[24]

In a single-blind study of COVID-19-induced telogen effluvium, QR678 Neo® significantly reduced shedding in most participants, with 87% achieving a negative pull test. QR678 Neo® led to a significantly improved hair count (mean=29.32; $P$=0.048). GPA scores demonstrated substantial improvement, even post-therapy. Similarly, patient self-assessment yielded high satisfaction scores for hair growth, hair appearance, and reduced scalp visibility. Three participants reported mild AEs.[25]

In a single-blind RCT involving 112 men undergoing hair transplantation, transplants with QR678 Neo® increased vellus and terminal hair counts, density, and shaft diameter compared to conventional transplantation ($P$<0.05). The QR678 Neo® group also demonstrated significantly higher GPA scores and terminal hair count (8.87 and 181.02, respectively; $P$<0.001). No AEs were reported.[7]

QR678 and QR678 Neo® exert their effects through intradermal delivery of recombinant and biomimetic growth factors, including VEGF, FGF, IGF-1, KGF, and copper tripeptide-1, which stimulate angiogenesis, promote anagen induction, and enhance follicular proliferation, in AGA and telogen effluvium.[9] These growth factors modulate key stages of the hair cycle and represent safe, accessible, and nonimmunogenic options for hair loss management.[9]

Grade of recommendation: C for the included QR678 and QR678 Neo® formulations for the treatment of hair loss based on 2 level 2b studies and 4 level 4 studies (Table 1).

**Clinical Recommendations**

Current evidence supports acetyl tetrapeptide-3, biotinoyl tripeptide-1, and glycyl-histidyl-lysine peptide formulations for hair growth therapy. The acetyl tetrapeptide-3 formulations received a Grade B recommendation (2 level 2b RCTs), with favorable follicular growth parameters and non-inferiority to 3% minoxidil. Biotinoyl tripeptide-1 formulations warrant a Grade B recommendation (1 level 2b and 2 level 4 studies), showing consistent improvements in hair density, shaft thickness, and anagen-to-telogen ratio. GHK/GHK-Cu formulations received a Grade B recommendation (2 level 1b RCTs) with clinically meaningful improvements, although replication in larger, diverse trials is needed to confirm efficacy. GPIGS similarly received a Grade B recommendation, but based on only a single level 2b RCT. In contrast, QR678 and QR678 Neo® are supported by more studies but lower levels of evidence (2 Level 2b and 4 Level 4 studies), justifying a Grade C recommendation. These formulations may be considered adjunctive in select clinical settings until higher-quality comparative data become available. Among the 12 clinical trials, 7 (58%) reported no adverse events, supporting the safety of peptide-based formulations.

## CONCLUSION

Peptides represent a promising therapeutic agent to address an unmet need for well-tolerated, effective treatments for hair loss and aesthetic improvement of hair appearance. Acetyl tetrapeptide-3, biotinoyl tripeptide-1, and glycyl-histidyl-lysine peptide-containing formulations demonstrated the most robust clinical data supporting their safe and effective use in hair growth. Limitations of this review include small sample sizes (n<50), multi-ingredient formulations that confound individual peptide effects, and varied outcome assessment, which limit inter-study comparisons. Further high-powered RCTs are needed to determine the independent efficacy of peptides for hair loss.

## DISCLOSURES

The authors report no conflicts of interest.

## ACKNOWLEDGMENT

LJ performed the literature search and wrote the main manuscript. LJ and KZ reviewed the studies independently. KZ and JJ helped to edit the final manuscript. All authors reviewed and approved the final manuscript.

## REFERENCES

1. Gudobba C, Mane T, Bayramova A, et al. Automating hair loss labels for universally scoring alopecia from images: rethinking alopecia scores. *JAMA Dermatol.* 2023;159(2):143-150. doi:10.1001/jamadermatol.2022.5415
2. Alessandrini A, Bruni F, Piraccini BM, Starace M. Common causes of hair loss - clinical manifestations, trichoscopy and therapy. *J Eur Acad Dermatol Venereol.* 2021;35(3):629-640. doi:10.1111/jdv.17079
3. Kumar V, Shome D, Atre S, et al. The iceberg phenomenon of alopecia associated public health ramifications on the quality of life among adults in India. *Dermatol Rev.* 2023;4:180-188. doi:10.1002/der2.109
4. Frith H, Jankowski GS. Psychosocial impact of androgenetic alopecia on men: a systematic review and meta-analysis. *Psychol Health Med.* 2024;29(4):822-842. doi:10.1080/13548506.2023.2242049
5. Sadick NS, Callender VD, Kircik LH, et al. New insight into the pathophysiology of hair loss trigger a paradigm shift in the treatment approach. *J Drugs Dermatol.* 2017;16(11):s135-s140.
6. Wu C-J, Yang C-Y, So PB, et al. Safety profile and efficacy of Biosea® revive serum for hair growth through in vitro assessment and clinical evaluation. *Cosmetics.* 2025;12(4):139. doi:10.3390/cosmetics12040139
7. Gold M, Zaman U, Chouksey V, Gosavi M. Evaluation of the efficacy of a biomimetic peptide solution for rejuvenation of donor scalp and as storage media for hair follicle grafts during FUE hair transplantation. *J Cosmet Laser Ther.* 2025;27(3):64-70. doi:10.1080/14764172.2025.2468499
8. Brezis M. Failing Public Health Again? Analytical Review of Depression and Suicidality From Finasteride. *J Clin Psychiatry.* 2025;86(4). doi:10.4088/JCP.25nr158629
9. Kapoor R, Shome D, Vadera S, et al. QR678 & QR678 neo hair growth formulations: a cellular toxicity & animal efficacy study. *Plast Reconstr Surg Glob Open.* 2020;8(8):e2843. doi:10.1097/gox.0000000000002843
10. Brinks AL, Needle CD, Kearney CA, et al. Hair transplant: patient candidacy, medical optimization, and surgical considerations. *Int J Dermatol.* 2026;65(2):245-256. doi:10.1111/ijd.17961
11. Kapoor R, Shome D, Vadera S, Ram MS. QR 678 & QR678 Neo Vs PRP-A randomised, comparative, prospective study. *J Cosmet Dermatol.* 2020;19(11):2877-2885. doi:10.1111/jocd.13398
12. Lee WJ, Sim HB, Jang YH, Lee SJ, Kim do W, Yim SH. Efficacy of a complex of 5-Aminolevulinic acid and glycyl-histidyl-lysine peptide on hair growth. *Ann Dermatol.* 2016;28(4):438-43. doi:10.5021/ad.2016.28.4.438
13. Lueangarun S, Panchaprateep R. An herbal extract combination (biochanin a, acetyl tetrapeptide-3, and ginseng extracts) versus 3% minoxidil solution for the treatment of androgenetic alopecia: a 24-week, prospective, randomized, triple-blind, controlled trial. *J Clin Aesthet Dermatol.* 2020;13(10):32-37.
14. Voiculescu V-M, Lupu M. Comparative study of a topical and oral combination therapy containing oleanolic acid, apigenin, and biotinyl tripeptide-1 in patients with androgenetic alopecia: a prospective, open-label trial. *Cosmetics.* 2025;12(4):152. doi:10.3390/cosmetics12040152
15. Loing E, Lachance R, Ollier V, Hocquaux M. A new strategy to modulate alopecia using a combination of two specific and unique ingredients. *J Cosmet Sci.* 2013;64(1):45-58.
16. Wongrakpanich A, Leanpolchareanchai J, Morakul B, et al. Phyllanthus emblica extract-loaded transfersomes for hair follicle targeting: phytoconstituents, characterization, and hair growth promotion. *J Oleo Sci.* 2022;71(7):1085-1096. doi:10.5650/jos.ess21425
17. Garre Contreras A, Piquero-Casals J, Trullas C, Martinez G. Efficacy and safety of a new topical hair loss-lotion containing oleanolic acid, apigenin, biotinyl tripeptide-1, diaminopyrimidine oxide, adenosine, biotin and ginkgo biloba in patients with androgenetic alopecia and telogen effluvium: a six-month open-label prospective clinical study. *J Cosmetol Tricol.* 01/01 2018;04doi:10.4172/2471-9323.1000132
18. Rinaldi F, Marzani B, Pinto D, Sorbellini E. Randomized controlled trial on a PRP-like cosmetic, biomimetic peptides based, for the treatment of alopecia areata. *J Dermatolog Treat.* 2019;30(6):588-593. doi:10.1080/09546634.2018.1544405
19. Choi HR, Kang YA, Ryoo SJ, et al. Stem cell recovering effect of copper-free GHK in skin. *J Pept Sci.* 2012;18(11):685-90. doi:10.1002/psc.2455
20. Iwabuchi T, Takeda S, Yamanishi H, et al. The topical penta-peptide Gly-Pro-Ile-Gly-Ser increases the proportion of thick hair in Japanese men with androgenetic alopecia. *J Cosmet Dermatol.* 2016;15(2):176-84. doi:10.1111/jocd.12216
21. Tsuruda A, Kawano Y, Maekawa T, Oka S. A short peptide GPIGS promotes proliferation of hair bulb keratinocytes and accelerates hair regrowth in mice. *Biol Pharm Bull.* 2005;28(3):485-489. doi:10.1248/bpb.28.485
22. Kapoor R, Shome D, Doshi K, Patel G, Vadera S. Evaluation of efficacy of QR 678 and QR678 neo hair growth factor formulation for the treatment of female pattern alopecia in patients with PCOS-A prospective study. *J Cosmet Dermatol.* 2020;19(10):2637-2646. doi:10.1111/jocd.13673
23. Kapoor R, Shome D. Intradermal injections of a hair growth factor formulation for enhancement of human hair regrowth - safety and efficacy evaluation in a first-in-man pilot clinical study. *J Cosmet Laser Ther.* 2018;20(6):369-379. doi:10.1080/14764172.2018.1439965
24. Clinic A, Asper A, Mittal A, et al. Evaluation of the safety and effectiveness of intradermal administration of QR678 Neo(®) hair growth factor formulation: A phase-IV, open-label, single-arm multi-ethnicity clinical trial. *J Cosmet Dermatol.* 2022;21(2):580-589. doi:10.1111/jocd.14715
25. Shome D, Kapoor R, Surana M, et al. Efficacy of QR678 Neo(®) hair growth factor formulation for the treatment of hair loss in Covid-19-induced persistent Telogen Effluvium-A prospective, clinical, single-blind study. *J Cosmet Dermatol.* 2022;21(1):16-23. doi:10.1111/jocd.14626
26. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009). https://www. cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009. Accessed November 9, 2025.

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ORIGINAL ARTICLE

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# Implementing Psoriatic Arthritis Screening and Dietary Interventions in Dermatology Practice: A Prospective Clinical Study

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## ABSTRACT

**Background:** Psoriatic arthritis (PsA) is a common, underdiagnosed inflammatory comorbidity of psoriasis (PsO) that can lead to irreversible joint damage without early intervention. Dermatologists are uniquely positioned to facilitate early PsA detection; however, routine screening remains inconsistent. Lifestyle interventions such as the Mediterranean diet (MD) may further enhance treatment outcomes when combined with biologic therapy.

**Methods:** This prospective, single-center, non-randomized controlled study evaluated routine PsA screening and treatment outcomes in an outpatient dermatology clinic. Adults with dermatologist-confirmed PsO were screened for PsA using the Psoriasis Epidemiology Screening Tool (PEST). Patients screening positive self-selected into biologic therapy alone or biologic therapy plus MD intervention. Pain severity was assessed at baseline and 1 month; logistic regression identified predictors of PsA screening positivity, and one-way ANOVA compared pain score changes among treatment groups.

**Results:** a total of 117 PsO patients were screened for PsA; 72 (61.5%) screened positive, representing a statistically significant increase compared with PsA detection prior to implementation of routine PEST screening ($P<0.001$).Pain severity was the only significant predictor of a positive PsA screen ($P<0.001$). Both guselkumab- and secukinumab-treated patients were evaluated with and without adherence to the MD; guselkumab combined with the MD demonstrated the greatest reduction in pain scores at 1 month compared with biologic therapy alone (mean change 3.13 ± 1.12; $P=0.01$).

**Conclusions:** Implementation of routine PsA screening in dermatology practice markedly increased PsA detection. Combining biologic therapy with dietary intervention was associated with greater short-term pain reduction, supporting the utility of lifestyle changes and counseling alongside pharmacologic management in PsA care.

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## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory disease that affects up to 30% of patients with psoriasis (PsO), corresponding to nearly 3 million individuals in the United States.[1,2] The annual incidence is estimated at 6 per 100,000 people, with a prevalence of 1 to 2 per 1,000, affecting men and women equally.[3] PsO is associated with a significant comorbidity burden, including increased risk of PsA, cardiovascular disease, inflammatory bowel disease, and psychological disorders, among others.[4] Patients frequently report impaired quality of life due to pain, fatigue, depression, social impairment, and disability, and up to 20% progress to irreversible joint damage and severe functional limitations without timely treatment.[5]

Dermatologists managing PsO are in a unique position to facilitate early PsA detection; however, screening strategies and implementation remain inconsistent. Studies show that up to 40% of dermatology providers do not routinely screen PsO patients for PsA, leading to delayed diagnosis and missed opportunities for early intervention.[6,7] Barriers include limited time during patient visits, lack of training in screening tools, and uncertainty regarding next steps or treatment modifications once PsA is suspected.[8,9] Validated, low-cost instruments such as the Psoriasis Epidemiological Screening Tool (PEST) offer an efficient means of identifying patients at risk,[10] yet are underutilized.

Advances in treatment have shifted the therapeutic landscape. While traditional immunosuppressants such as methotrexate and sulfasalazine remain in use, biologic therapies targeting cytokines such as TNF, IL-17, and IL-23 are now endorsed as first-line therapy by both dermatology and rheumatology societies.[11,12] Lifestyle interventions, particularly anti-inflammatory diets and weight reduction, have also demonstrated benefits in managing PsO and PsA, including reduced pain, improved metabolic outcomes, and enhanced overall quality of life.[13,14] Integrating dietary counseling with pharmacologic therapy may therefore represent a cost-effective and sustainable approach to optimize patient outcomes.

The present study aims to evaluate the impact of implementing routine PsA screening in a private dermatology practice, to compare the effectiveness of combining biologic therapy with an anti-inflammatory diet, and to identify demographic and clinical predictors of PsA detection. **To obtain copies of additional materials that are mentioned further in this article, such as the standardized script, Data Information Sheet, Mediterranean diet materials, and script call, please reach out to the corresponding author.*

## MATERIALS AND METHODS

### Study Design, Setting, and Eligibility

This prospective, single-center, non-randomized controlled trial was conducted at an outpatient dermatology clinic in Southeast Tennessee. The clinic staff included 2 board-certified dermatologists, 2 nurse practitioners, and 1 physician assistant. The primary aims of this study were threefold: (1) to assess the effectiveness of the Psoriasis Epidemiology Screening Tool (PEST) in identifying patients with psoriatic arthritis (PsA) among those with psoriasis (PsO); (2) to evaluate whether demographic and clinical variables (age, gender, ethnicity, marital status, and pain severity) predict a positive PsA screening; and (3) to determine whether the addition of the Mediterranean diet (MD) to standard biologic therapy yields greater pain reduction compared with pharmacologic therapy alone. Patients were eligible for inclusion if they: (1) were aged ≥18 years; (2) had a dermatologist-confirmed diagnosis of PsO; (3) reported English as their primary language; (4) could read and write in English; and (5) were available for follow-up at 1 month.

### Screening and Recruitment

All eligible patients were administered the PEST questionnaire to screen for PsA. A total of 117 patients with psoriasis were screened, of whom 72 (61.5%) screened positive for PsA. Of these, 71 (99%) elected to enroll and self-selected into 1 of 4 treatment arms. Patients were then assessed for pain severity using the Wong-Baker FACES Pain Rating Scale (WBFPRS), which measures pain on a scale from 0 (no pain) to 10 (worst pain). Study details were explained to potential participants using a standardized script* to ensure uniform recruitment. Informed consent was obtained, and participants completed a Data Information Sheet*.

### Intervention and Control Groups

Participants chose between 2 treatment arms: biologic therapy alone or biologic therapy in combination with dietary modification. Those opting for the combination approach received instruction on the MD, guided by a script and supplementary materials including a shopping list, diet compliance calendar, and MD pyramid.*

There were 4 treatment groups:

- Group 1 (n = 11): Secukinumab 300 mg subcutaneous injections weekly for 1 month followed by monthly dosing thereafter + MD
- Group 2 (n = 24): Guselkumab 100 mg subcutaneous injection once monthly + MD
- Group 3 (n = 7): Secukinumab alone
- Group 4 (n = 14): Guselkumab alone

Secukinumab and guselkumab were selected for their favorable safety profiles, ease of home administration, broad insurance coverage, and sample availability in-office. Medication selection was determined by provider experience and insurance coverage. All patients initiated therapy at the time of enrollment.

### Provider Training and Standardization

Providers received training in PEST administration through one-on-one sessions with the principal investigator, including a review of American College of Rheumatology (ACR) criteria and relevant literature. Additional group training sessions were held in December 2021 and again following IRB approval in March 2022. Providers were instructed to use only standardized scripts and respond to all patient questions uniformly.

### Follow-Up and Compliance Monitoring

Patients in the dietary intervention arms were contacted 1-week post-enrollment using a scripted call* to reinforce dietary compliance and address concerns. Up to 3 attempts were made if the patient did not answer initially. These patients also tracked compliance using the MD Calendar by marking diet-compliant meals with hash marks.

At 1 month, all study participants returned for follow-up. Pain was reassessed using the WBFPRS. MD Calendars were reviewed, and adherence was considered satisfactory if ≥50% of meals were compliant. Patients were also asked about medication side effects.

### Outcomes and Statistical Analysis

The primary outcomes were: (1) proportion of PsO patients screening positive for PsA using the PEST tool; (2) change in WBFPRS scores from baseline to 1 month; and (3) dietary compliance in the intervention groups.

A chi-square ($\chi^2$) Goodness of Fit test evaluated the change in PsA detection rates pre- and post-implementation of PEST. Logistic regression was used to assess predictors of a positive

PsA screen based on demographic and clinical variables. A one-way ANOVA compared mean pain score changes among the 4 treatment groups. Post-hoc analysis was conducted to determine differences between the intervention and control groups.

## RESULTS

The average age of our 117 PsO patient population was 52 years old and exhibited a female (54.7%) and white (92.4%) predominance, with 5.4%, 1.2%, and 1.0% identifying as black, Hispanic, and Asian, respectively. A non-parametric one-sample chi-square test was run to compare the proportion of positive PsA diagnoses using the PEST screening tool to the proportion of PsA diagnoses prior to PEST screening for patients with PsO. Before the PEST screening tool, 16 cases of PsA were diagnosed out of 1,261 total patients seen in the clinic, from January 1, 2021 to March 12, 2022. When PEST screening was initiated for the identified 117 PsO patients, 72 (61.5%) were diagnosed with PsA. A chi-square $\chi^2$ goodness-of-fit test demonstrated a statistically significant difference in the proportion of PsO patients diagnosed with PsA using the PEST screening tool compared with the proportion diagnosed without PEST screening; $\chi^2$ (1) = 3436.835, $P$<0.001 (Table 1).

The patients who screened positive for PsA using the PEST were invited to participate in the treatment arm of this study. Seventy-one (71) patients accepted the offer, and of these, 47 expressed willingness to use diet modification with pharmacology for treatment of their PsA. Of these 47 patients, 25% were deemed non-compliant by the PI at the 1-month follow-up visit discussion and diet calendar review and were excluded from final statistical analysis. A total of 35 eligible participants were included in the intervention arm.

One-way ANOVA analysis showed a statistically significant difference in mean pain scores before and after treatment regimens among the 4 different therapy regimens. Baseline mean pain scores were highest in groups 2 (Guselkumab + Diet) and 4 (Guselkumab alone). After 1 month of treatment, one-way ANOVA with post-hoc analysis showed that guselkumab combined with the MD resulted in the greatest reduction in pain scores (mean change 3.13 ± 1.12; $P$=0.01) compared with the other 3 treatment groups (Table 2, Figure 1). Smaller, non-statistically significant reductions were observed with secukinumab plus MD (2.64 ± 1.21), secukinumab alone (3.00 ± 2.16), and guselkumab alone (1.86 ± 0.77) (Table 2).

To test the probability of predicting a positive PsA among the selected variables, logistic regression was used. When assessing baseline pain as well as demographic variables, including age, gender, marital status, and race, pain was found to be the only significant predictor of PsA diagnosis; B(1) = -1.116, $P$=<.001 (Table 3).

**TABLE 1.**

**Comparison of PsA Rates Before and After the Use of PEST Screening Tool**

| Group | PsA negative N (%) | PsA positive N (%) | $X^2$ | *P* |
|---|---|---|---|---|
| Before PEST implementation | 1245 (99.9) | 16 (0.01) | 3436.84 | 0.001 |
| After PEST implementation | 45 (38.5) | 72 (61.5) | | |

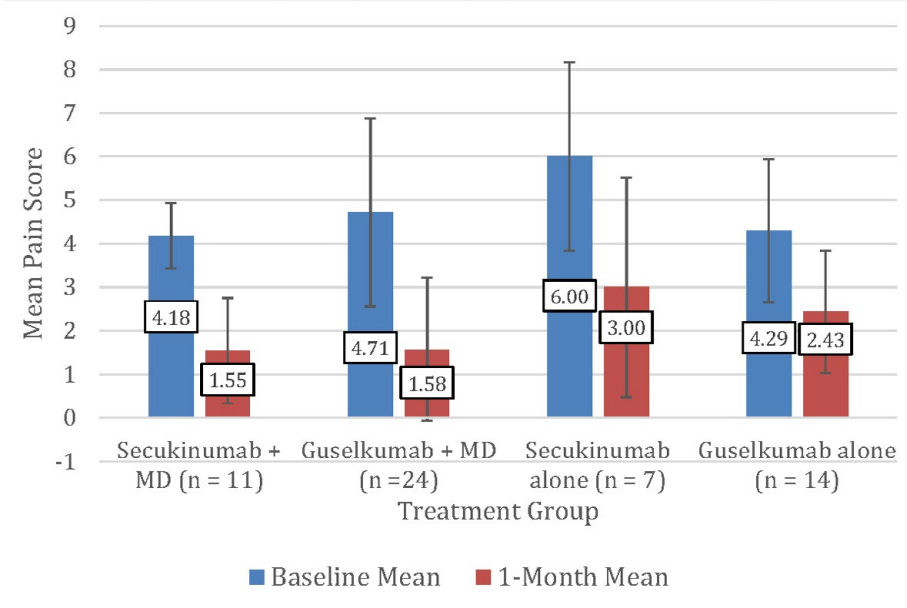
**TABLE 2.**

**Mean Pain Score Differences Among 4 Treatment Groups at Initial Visit and at 1 Month Post Treatment Initiation**

| Group (n) | Baseline pain (SD) | 1 month pain (SD) | Pain Change (SD) | F (df) | *P* |
|---|---|---|---|---|---|
| 1 (11) | 4.18 (0.75) | 1.55 (1.21) | 2.64 (1.21) | -- | -- |
| 2 (24) | 4.71 (2.16) | 1.58 (1.64) | 3.13 (1.12) | -- | -- |
| 3 (7) | 6.00 (2.16) | 3.00 (2.52) | 3.00 (2.16) | -- | -- |
| 4 (14) | 4.29 (1.64) | 2.43 (1.40) | 1.86 (0.77) | -- | -- |
| Total 56 | -- | -- | 2.69 (0.17) | 3.29 (3,52) | 0.028 |

Group 1: Secukinumab + MD
Group 2: Guselkumab + MD
Group 3: Secukinumab alone
Group 4: Guselkumab alone

**FIGURE 1.** Mean pain score changes among 4 treatment groups at initial visit and at 1 month post treatment initiation.




Note: Post-hoc comparisons using the Bonferroni test indicated that there was a significant difference only between Group 2 (Guselkumab + MD) and Group 4 (Guselkumab alone), with the mean score for Group 2 being 3.13 (SD = 1.12), *P*=0.01.

**TABLE 3.**

**Logistic Regression Analyses of Predicting Factors for Psoriatic Arthritis**

| | B | S.E. | Wald | df | *P*-Value | Exp(B) |
|---|---|---|---|---|---|---|
| First Pain | -1.116 | 0.226 | 24.330 | 1 | <.001 | 0.328 |
| Gender | 0.196 | 0.331 | 0.353 | 1 | 0.552 | 1.217 |
| Age | 0.019 | 0.020 | 0.965 | 1 | 0.326 | 1.019 |
| Single | -0.209 | 0.614 | 0.116 | 1 | 0.734 | 0.812 |
| Married | -1.013 | 1.169 | 0.751 | 1 | 0.386 | 0.363 |
| Divorced | -0.393 | 1.571 | 0.063 | 1 | 0.803 | 0.675 |
| White | -16.670 | 26641.07 | 0.000 | 1 | 1.000 | 0.000 |
| Black | -0.036 | 1.116 | 0.001 | 1 | 0.975 | 0.965 |
| Hispanic | 19.202 | 26429.84 | 0.000 | 1 | 0.999 | 21838109 |
| Constant | 4.660 | 2.168 | 4.619 | 1 | 0.032 | 105.630 |

## DISCUSSION

This study demonstrates a significant increase in patients who were diagnosed with PsA following the implementation of the PEST screening tool in a dermatology clinic. While only 16 PsA cases were diagnosed in a 15-month period prior to the project, 72 PsO patients screened positive for PsA in only a 3-month period, indicating the utility of the PEST. Ultimately, our results found that Guselkumab in combination with the MD significantly decreased patient-reported pain. Interestingly, pain was found to be the only significant predictor for PsA diagnosis.

The high rate of PsA detection observed in this patient cohort following the implementation of the PEST is consistent with high rates of PsA underdiagnosis reported in the literature. While the overall prevalence of PsA in patients with PsO is 20%,[15] up to 41% of patients not actively under the care of a rheumatologist have undiagnosed PsA.[16] To address this gap, the International Dermatology Outcome Measures (IDEOM) group has developed a clinical framework integrated into the electronic medical record (EMR) using the PEST and Psoriatic Arthritis Impact of Disease questionnaire (PsAID-12) to streamline PsA screening,

symptom assessment, and specialist referral.[17] Taken together, these results underscore the importance of screening all PsO patients for PsA using a validated tool in the dermatology clinic setting.

Previous research has shown a statistically significant inverse association between MD adherence and PsO severity, independent of confounders such as BMI and comorbidities.[18] The anti-inflammatory and antioxidant properties of the diet, as well as its favorable effects on the gut microbiome, are hypothesized as driving factors.[18,19] When specifically investigating its effects on PsA, Katsimbri et al have shown that adherence to the MD correlates with reduced disease activity scores, decreased inflammatory markers, and improved joint and skin outcomes, even after adjusting for BMI.[20] Notably, this study also incorporated adherence to exercise regimens, which our study did not account for.

In 2018, the National Psoriasis Foundation (NPF) published the following dietary recommendations: hypocaloric diets in overweight or obese patients, gluten-free diets in patients who test positive for serologic markers of gluten sensitivity, and weakly recommended vitamin D supplementation in patients with PsA.[21] While these initial recommendations are based on low-quality data, there have since been more original studies, including our analysis, which support the use of the MD for patients with PsO.[22]

However, this study is not without limitations. Weight loss as a major confounder complicates the interpretation of many dietary studies. Since obesity independently worsens psoriasis severity and weight reduction alone improves outcomes, distinguishing whether benefits arise from specific dietary components vs caloric restriction remains challenging.[23] Additionally, high patient dropout rates amongst dietary intervention studies create significant attrition bias.[23] In our study, high non-compliance initially seen in the dietary intervention arm, lack of randomization between treatment groups, and absence of blinding introduce potential bias. Treatment assignment was also constrained by insurance formularies and product sample availability, leading to a disproportionately larger Guselkumab group and potentially more favorable outcomes. The planned 1-week follow-up phone calls reached only 10% of participants in the intervention arm due to difficulty contacting patients, limiting follow-up analysis. The overall sample size was small, and the study population was predominantly White, reflecting regional demographics and limiting generalizability of the findings.

Overall, our results promote the need for increased PsA screening conducted by dermatology providers as well as the utility of the MD as an adjunctive intervention to medical PsA treatment. Future research should further examine the use of integrated PsA screening into the EMR, the efficacy of different dietary interventions over longer follow-up periods and investigate the potential benefits of combining emerging biologic therapies with broader lifestyle interventions.

## DISCLOSURES

SR, BC, RR, KL, WR have no conflicts of interest to disclose. VC has served on the Speaker's Bureau for AbbVie, Arcutis Biotherapeutics, Beiersdorf, Galderma, Johnson & Johnson, Lilly, Sanofi/Regeneron, Sun Pharma, and UCB, and as an advisory board member for Incyte and Novartis. ABG has received honoraria for serving as a consultant, advisory board member, speaker, or faculty participant for AbbVie, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Novartis, Oruka Therapeutics, Sanofi, Sun Pharmaceutical Industries Ltd., Takeda Pharmaceuticals USA Inc., and UCB. She has served on a Data Safety Monitoring Board for AbbVie. ABG has received research funding or investigator-initiated grants from Bristol Myers Squibb, Janssen, MoonLake Immunotherapeutics, Sanofi, and UCB, with all research funds paid directly to her institution.

**IRB status:** Approved by Graceland University IRB.

## REFERENCES

1. Bagel J, Schwartzman S. Enthesitis and dactylitis in psoriatic disease: a guide for dermatologists. *Am J Clin Dermatol.* 2018;19(6):839-852. doi:10.1007/s40257-018-0377-2
2. Perez-Chada LM, Gottlieb AB, Cohen J, et al. Measuring psoriatic arthritis symptoms: a core domain in psoriasis clinical trials. *J Am Acad Dermatol.* 2020;82(1):54-61. doi:10.1016/j.jaad.2019.05.075
3. Barnas JL, Ritchlin CT. Etiology and pathogenesis of psoriatic arthritis. *Rheum Dis Clin North Am.* 2015;41(4):643-663. doi:10.1016/j.rdc.2015.07.006
4. Daugaard C, Iversen L, Hjuler KF. Comorbidity in adult psoriasis: considerations for the clinician. *Psoriasis (Auckl).* 2022;12:139-150. doi:10.2147/ptt.S328572
5. Giannelli A. A review for physician assistants and nurse practitioners on the considerations for diagnosing and treating psoriatic arthritis. *Rheumatol Ther.* 2019;6(1):5-21. doi:10.1007/s40744-018-0133-3
6. Iragorri N, Hazlewood G, Manns B, et al. Psoriatic arthritis screening: a systematic review and meta-analysis. *Rheumatology (Oxford).* 2019;58(4):692-707. doi:10.1093/rheumatology/key314
7. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol.* 2021;84(2):432-470. doi:10.1016/j.jaad.2020.07.087
8. Urruticoechea-Arana A, Benavent D, León F, et al. Psoriatic arthritis screening: a systematic literature review and experts' recommendations. *PLoS One.* 2021;16(3):e0248571. doi:10.1371/journal.pone.0248571
9. Mathew AJ, Chandran V. Depression in psoriatic arthritis: dimensional aspects and link with systemic inflammation. *Rheumatol Ther.* 2020;7(2):287-300. doi:10.1007/s40744-020-00207-6
10. Chang J, Litvinov IV, Ly C, et al. Utilization of the Psoriasis Epidemiology Screening Tool (PEST): a risk stratification strategy for early referral of psoriatic arthritis patients to minimize irreversible erosive joint damage. *J Cutan Med Surg.* 2022;26(6):600-603. doi:10.1177/12034754221128796
11. Singh JA, Guyatt G, Ogdie A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol.* 2019;71(1):5-32. doi:10.1002/art.40726
12. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* 2020;79(6):700-712. doi:10.1136/annrheumdis-2020-217159

13. Lăcătușu CM, Grigorescu ED, Floria M, et al. The Mediterranean diet: from an environment-driven food culture to an emerging medical prescription. Int *J Environ Res Public Health*. 2019;16(6). doi:10.3390/ijerph16060942
14. Vaduva OG, Periferakis AT, Doncu RE, et al. Dietary principles, interventions and oxidative stress in psoriasis management: current and future perspectives. *Medicina (Kaunas)*. 2025;61(7). doi:10.3390/medicina61071296
15. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol*. 2019;80(1):251-265. e19. doi:10.1016/j.jaad.2018.06.027
16. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol*. 2013;69(5):729-735. doi:10.1016/j.jaad.2013.07.023
17. Romanelli S, Ball GD, Hamade H, et al. Streamlining psoriatic arthritis screening and management using the IDEOM clinical framework: a quality improvement initiative. *J Drugs Dermatol*. 2025;24(8):777-781. doi:10.36849/jdd.9210
18. Phan C, Touvier M, Kesse-Guyot E, et al. Association between Mediterranean anti-inflammatory dietary profile and severity of psoriasis: results from the NutriNet-Santé cohort. *JAMA Dermatol*. 2018;154(9):1017-1024. doi:10.1001/jamadermatol.2018.2127
19. Kupczyk D, Bilski R, Szeleszczuk Ł, et al. The role of diet in modulating inflammation and oxidative stress in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. *Nutrients*. 2025;17(9). doi:10.3390/nu17091603
20. Katsimbri P, Grivas A, Papadavid E, et al. Mediterranean diet and exercise are associated with better disease control in psoriatic arthritis. *Clin Rheumatol*. 2024;43(9):2877-2887. doi:10.1007/s10067-024-07080-6
21. Ford AR, Siegel M, Bagel J, et al. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the Medical Board of the National Psoriasis Foundation: a systematic review. *JAMA Dermatol*. 2018;154(8):934-950. doi:10.1001/jamadermatol.2018.1412
22. Leung A, Kranyak A, Marquez-Grap G, et al. Nutrition and psoriasis: the latest evidence and how to approach nutrition in clinical practice. *Am J Clin Dermatol*. 2025. doi:10.1007/s40257-025-00992-2
23. Ko SH, Chi CC, Yeh ML, et al. Lifestyle changes for treating psoriasis. *Cochrane Database Syst Rev*. 2019;7(7):Cd011972. doi:10.1002/14651858.CD011972.pub2

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JDD

**F AROUND AND FIND OUT: FAILING FORWARD, IL-17F IN FOCUS, AND FINDING NEW TREATMENT PARADIGMS AND FRIENDSHIPS THROUGH INDUSTRY COLLABORATIONS**

For too long, the therapeutic ladder in hidradenitis suppurativa has often looked less like a ladder and more like an uneven mound: try this, fail that, wait, escalate, repeat. But while we are waiting, HS certainly isn't. Inflammation marches on, tunnels form, scars accumulate, and what was potentially preventable disease becomes permanent architectural damage. So perhaps the better question isn't when has the patient failed enough to earn advanced therapy, but rather when do we have enough evidence to justify waiting? JDD Podcast host Dr. Adam Friedman is joined by Dr. Tae Oh, Head of Medical Affairs for Dermatology in the US at UCB, to challenge the conventional "save it for later" mentality and examine how our evolving understanding of HS pathogenesis should reshape the treatment paradigm.

Tune in as they go beyond the bottle to explore industry's role moving past the molecule. Can therapeutic development help expose the true prevalence and burden of an underrecognized disease? What responsibilities do industry partners have in disease awareness, education, evidence generation, patient identification, and ultimately defining not simply whether a therapy works, but when it should be used? Then it's down to the follicular unit. Drs. Friedman and Oh dig into what our evolving understanding of HS initiation and propagation means at the bedside. If inflammation ultimately contributes to irreversible tunnels, scarring, pain, and disfigurement, is there a window of opportunity when earlier intervention could alter the trajectory before inflammatory disease becomes structural disease? And finally, the uncomfortable question...Are we making patients fail their way toward effective treatment? From therapeutic inertia and payer barriers to biologics, procedures, disease modification, and the consequences of undertreatment, this episode challenges one of medicine's most persistent assumptions, that doing less first is inherently safer or smarter.



HOST
Dr. Adam Friedman



GUEST
Dr. Tae Oh

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Bruton Tyrosine Kinase Inhibitors for Systemic Lupus Erythematosus: A Systematic Review of Randomized Controlled Trials

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## ABSTRACT

**Background:** Systemic lupus erythematosus (SLE) is a chronic relapsing autoimmune disease with frequent cutaneous involvement and unmet treatment need. Given safety and efficacy concerns with first-line therapies and no US Food and Drug Administration (FDA)-approved treatment for cutaneous lupus erythematosus (CLE), Bruton tyrosine kinase (BTK) has emerged as a biologically relevant target.

**Methods:** On January 20, 2026, PubMed, Embase, and Cochrane Library were searched per PRISMA guidelines. Clinical trials investigating BTK inhibitors for the treatment of SLE were included.

**Results:** Of 579 records, 5 randomized clinical trials met inclusion criteria, evaluating elsubrutinib (2), evobrutinib (1), fenebrutinib (1), and orelabrutinib (1). Efficacy across SLE endpoints was variable. Elsubrutinib- and orelabrutinib-based regimens improved cutaneous disease. Evobrutinib and fenebrutinib showed limited or nonsignificant differences in primary endpoints compared with placebo. Safety was generally acceptable; adverse events included infections and elevations in transaminase levels.

**Conclusions:** BTK inhibitors showed variable efficacy in SLE but potential for cutaneous disease improvement. To date, no clinical trials have evaluated BTK inhibition in CLE. Given promising clinical and mouse model data, dedicated CLE-focused randomized controlled trials are warranted.

*J Drugs Dermatol.* 2026;25(11):1039-1044. doi:10.36849/JDD.10039

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with frequent relapses and multisystem involvement, including the joints, kidneys, heart, lungs, central nervous system, and commonly the skin.[1] SLE impacts more than 200,000 Americans and 3.4 million worldwide, with a projected global market >$4 billion by 2030.[1-4]

Cutaneous involvement is a common manifestation of SLE, impacting >80% of patients.[1] Cutaneous lupus erythematosus (CLE) comprises acute, subacute, and chronic subtypes, with variable clinical features and risk of progression to SLE.[1] Acute CLE presents in a malar or maculopapular pattern, occurring in up to 50% of SLE patients.[5] Subacute CLE is a photosensitive annular or papulosquamous eruption observed in 10% to 15% of SLE patients.[5] CLE commonly presents as discoid lupus with scaly, erythematous macules or papules that progress to indurated plaques; other chronic CLE manifestations include lupus erythematosus profundus (lupus panniculitis), chilblain lupus erythematosus, and lupus erythematosus tumidus.[5,6] Nearly 30% of patients with DLE progress to SLE, and these patients often require systemic therapy.[5,6] Notably, there are no US Food and Drug Administration (FDA)-approved therapies for CLE, highlighting a substantial therapeutic unmet need.

Treatment of SLE relies on immunosuppression to prevent flares and modulate systemic involvement.[1] Hydroxychloroquine (HCQ) is a systemic therapy for CLE and SLE.[1] However, HCQ can be associated with adverse events (AEs), including cardiotoxicity, neuromyotoxicity, hyperpigmentation, and vision loss.[7] HCQ use may yield incomplete response (~50%) and flares.[6] Given toxicity and efficacy concerns, there remains a clear need for safer, more effective SLE therapies.

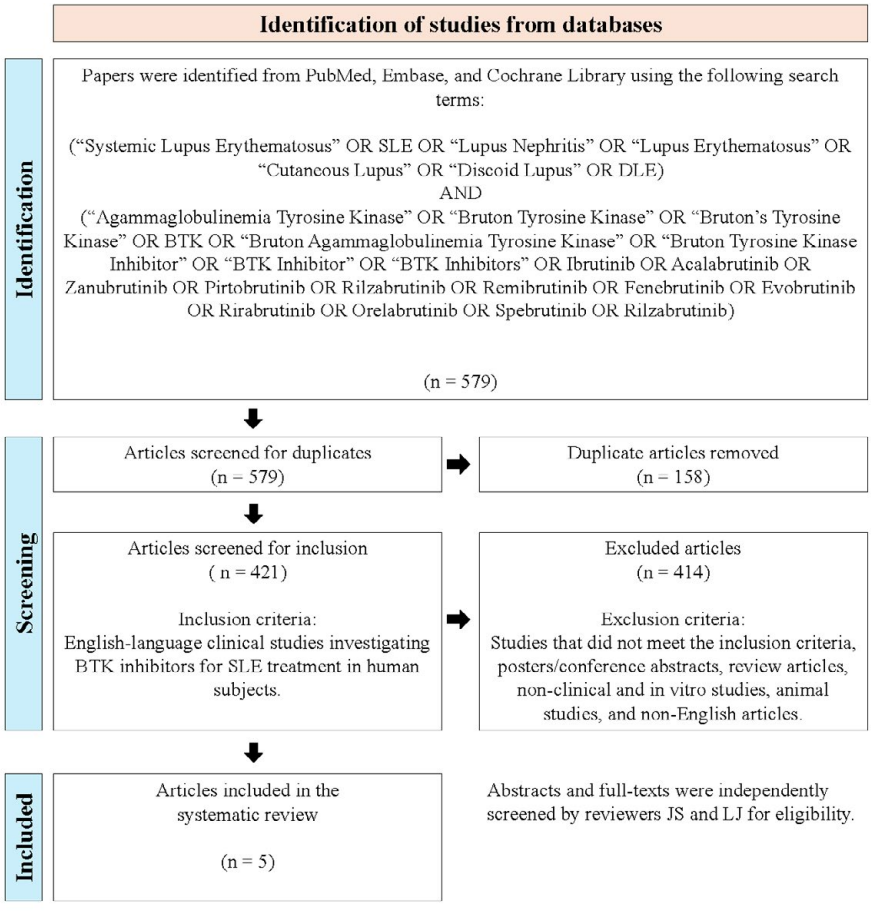
The pathophysiology of SLE is multifactorial, with dysregulated B- and T-cells central to disease pathogenesis and key therapeutic targets.[8] B-cell dysregulation drives disease through loss of tolerance to self-antigens, generating pathogenic autoantibodies, immune complex deposition, complement activation, and multiorgan damage.[1] Reduced B-cell receptor signaling, including impaired tolerance and lowered activation thresholds, promotes abnormal stimulation of auto-

**TABLE 1.**

**Summary of Studies Meeting Inclusion Criteria for the Use of BTK Inhibitors for the Treatment of Systemic Lupus Erythematosus**

| Author (Year) | Subjects | Intervention | Duration | Findings | Adverse Events |
|---|---|---|---|---|---|
| **Elsubrutinib** | | | | | |
| Merrill (2024)[15] | 341 participants | Taken orally:<br>• Elsubrutinib 60 mg and upadacitinib 30 mg QD (ABBV-599 high dose)<br>• Elsubrutinib 60 mg and upadacitinib 15 mg QD (ABBV-599 low dose)<br>• Elsubrutinib 60 mg QD<br>• Upadacitinib 30 mg QD<br>• Placebo | 48 weeks | • Higher CLASI-50 response rates with ABBV-599 high dose cadompared with placebo at week 24 and upadacitinib 30 mg compared with placebo at week 48<br>• Greater proportion of patients achieved SRI-4 and glucocorticoid dose ≤10 mg QD at week 24, with upadacitinib (54.8%) and ABBV-599 high dose (48.5%) versus placebo (37.3%)<br>• SRI-4, BICLA, and LLDAS responses higher with ABBV-599 high dose and upadacitinib compared with placebo at weeks 24 and 48<br>• ABBV-599 high dose and upadacitinib 30 mg significantly improved flare incidence and time to first flare through week 48 compared with placebo | • Incidence TEAEs was lower in the ABBV-599 high dose group (10.3%) than in the upadacitinib 30 mg (21.0%) or placebo (17.3%) groups<br>• AEs in patients receiving ABBV-599 high dose and upadacitinib 30 mg included nonfatal strokes, not attributed to the study drugs, and increased incidence of serious infections in patients with underlying risk factors for infection<br>• Higher incidence of herpes zoster infections in the ABBV-599 high dose and upadacitinib 30 mg groups than placebo<br>• Three deaths unrelated to the study drug |
| Merrill (2025)[14] | 185 participants | Taken orally:<br>• Elsubrutinib 60 mg and upadacitinib 30 mg QD (ABBV-599 high dose)<br>• Upadacitinib 30 mg QD<br>• ABBV-599 high dose (originally placebo group) | 104 weeks | • Increased proportion of patients who achieved CLASI-50 (100%, 88.9%, and 100% of patients in the upadacitinib 30 mg, ABBV-599 high dose, and placebo to ABBV-599 high dose groups, respectively)<br>• In the upadacitinib 30 mg and ABBV-599 high dose groups, the proportion of patients achieving SRI-4, BICLA, and LLDAS responses was sustained through week 104<br>• Daily glucocorticoid dose decreased from week 0 to week 104 in all treatment groups<br>• The incidence of overall flares through 104 was maintained in the upadacitinib 30 mg group and decreased in the ABBV-599 high dose and placebo to ABBV-599 high dose groups | • Exposure-adjusted TEAEs were highest in the placebo to ABBV-599 high dose group<br>• Rates of exposure-adjusted serious AEs were low across all groups, with no deaths<br>• Only 1/5 serious infections (limb abscess) was considered related to upadacitinib<br>• Herpes zoster occurred across all groups, and one patient in the upadacitinib 30 mg group developed hypogammaglobulinemia |
| **Evobrutinib** | | | | | |
| Wallace (2023)[12] | 469 participants | Taken orally:<br>• Evobrutinib 25 mg QD<br>• Evobrutinib 75 mg QD<br>• Evobrutinib 50 mg BD<br>• Placebo | 52 weeks | • No statistically significant differences between evobrutinib groups and placebo in general SRI-4 response, SRI-4 response in the serologically active subpopulation, and SRI-6 response in HDA subpopulation<br>• Compared with placebo, evobrutinib 75 mg QD demonstrated longer time to first BILAG A flare<br>• No clinically meaningful differences between evobrutinib and placebo in organ-specific disease activity, flare rate, health-related quality of life, corticosteroid usage, or SLE serum markers | • All doses of evobrutinib were well tolerated<br>• TEAE rates were similar between treatment groups, most commonly ALT, AST, amylase, and lipase, as well as lymphopenia, noncardiac chest pain, otitis media, and headache<br>• Two deaths occurred in the HDA subgroup; investigators only reported bone marrow failure as treatment-related<br>• 121 (25.8%) participants who discontinued treatment were generally balanced across treatment groups, and most commonly discontinued due to an AE such as increased ALT or AST (n=64), lack of efficacy (n=13), or loss to follow-up (n=9) |
| **Fenebrutinib** | | | | | |
| Isenberg (2021)[18] | 260 participants | Taken orally<br>• Fenebrutinib 150 mg QD<br>• Fenebrutinib 200 mg BD<br>• Placebo | 48 weeks | • SRI-4 response rates slightly higher for fenebrutinib 150 mg QD and fenebrutinib 200 mg BD (51% and 52%, respectively) compared with placebo (44%), without between-group statistical significance<br>• BICLA response rates were 53% with fenebrutinib 150 mg QD, 42% with fenebrutinib 200 mg BD, and 41% with placebo<br>• No differences between treatment groups for time to flare<br>• Relative to placebo, fenebrutinib was associated with reductions in anti-double-stranded DNA autoantibodies, BTK-dependent plasmablast RNA signature, total IgG, and IgM, along with increased C4 levels | • More patients in the fenebrutinib 200 mg BD group reported serious AEs and experienced AEs that led to treatment withdrawal than the fenebrutinib 150 mg QD and placebo groups<br>• One death occurred in the fenebrutinib 150 mg group (salivary gland neoplasm)<br>• The treatment groups developed similar infection and serious infection rates<br>• More patients in the fenebrutinib 200 mg BD group also experience elevations in AST and ALT levels than other treatment arms |
| **Fenebrutinib** | | | | | |
| Li (2025)[19] | 60 participants | Taken orally:<br>• Orelabrutinib 50 mg<br>• Orelabrutinib 80 mg<br>• Orelabrutinib 100 mg<br>• Placebo | 12 weeks | • SRI-4 response rates were 50%, 62%, and 64% with orelabrutinib 50 mg, 80 mg, and 100 mg, respectively, versus 36% with placebo<br>• In the subgroup of participants with baseline SLEDAI-2K >8, SRI-4 responses were significantly higher with orelabrutinib 50 mg (80%), 80 mg (83%), and 100 mg (100%) in comparison with placebo (0%)<br>• Rash remission rates based on SLEDAI-2K were 40%, 75%, and 36% with orelabrutinib 50 mg, 80 mg, and 100 mg, respectively, versus 33% with placebo | • Most AEs were mild-to-moderate with 3/6 serious AEs being treatment-related<br>• At least one TEAE occurred in 80%, 93%, and 100% of patients receiving orelabrutinib 50 mg, 80 mg, and 100 mg once daily, respectively, compared with 86% of patients taking placebo<br>• AEs included upper respiratory tract infection, decreased lymphocyte count, anemia, and abnormal liver function<br>• No deaths occurred, and AE-related treatment discontinuation was infrequent |

**FIGURE 1.** PRISMA flow diagram for the systematic review of BTK Inhibitors for the treatment of SLE.




reactive B-cells.[8] In CLE, B cells drive autoantibody-mediated immune-complex deposition at the dermal-epidermal junction, promoting complement activation and chronic skin injury.[9] B-cell dysregulation is a central driver of disease pathogenesis and provides a strong mechanistic basis for B-cell-targeted therapeutic strategies, such as belimumab, which is FDA-approved for SLE management.

Bruton tyrosine kinase (BTK) is a key messenger in the B-cell receptor signaling pathway, necessary for B-cell activation and differentiation.[8,10] BTK is also involved in signaling pathways in innate immune cells, including monocytes and macrophages, and contributes to cutaneous inflammation in SLE.[10] Peripheral blood B cells in SLE patients exhibit higher BTK expression than those from healthy controls, and expression correlates with established disease-severity markers, including SLE Disease Activity Index, anti-double-stranded DNA antibody levels, 24-hour proteinuria, and lupus nephritis.[11,12] Although initially identified as a genetic mutation causing X-linked agammaglobulinemia, BTK's multifaceted role in B-cell function makes it a promising therapeutic target for other B-cell disorders, including SLE and CLE.[10] Murine models and clinical trials investigating BTK inhibitors for SLE suggest potential benefits for systemic and cutaneous disease activity.[10] Herein, we summarize the safety and efficacy of BTK inhibitors for the treatment of SLE.

## MATERIALS AND METHODS

On January 20, 2026, Embase, PubMed, and Cochrane Library were systematically searched according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines (Figure 1).

## RESULTS

The systematic search yielded 579 papers. After title, abstract, and full-text screening by LJ and JS, 5 randomized controlled trials (RCTs) met the inclusion criteria. These studies evaluated formulations with the following BTK inhibitors: elsubrutinib (2), evobrutinib (2), fenebrutinib (1), and orelabrutinib (1).

## DISCUSSION

**Elsubrutinib**

Elsubrutinib is an investigational, oral, selective, and irreversible BTK inhibitor developed for autoimmune diseases, including SLE and rheumatoid arthritis, that inhibits B-cell activation and modulates immune complex-based inflammation.[13] Elsubrutinib

has been studied in combination with upadacitinib (ABBV-599) to target the Janus Kinase 1 (JAK1) pathway in addition to BTK.[14,15]

We identified 2 RCTs evaluating oral elsubrutinib-based therapy for SLE. In a 48-week, phase 2 RCT, 341 patients with SLE were divided into 5 groups: (1) elsubrutinib 60 mg and upadacitinib 30 mg once daily (QD) (ABBV-599 high dose), (2) elsubrutinib 60 mg and upadacitinib 15 mg QD (ABBV-599 low dose), (3) elsubrutinib 60 mg QD, (4) upadacitinib 30 mg QD, or (5) placebo. Among patients with baseline Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity scores ≥10, CLASI-50 response rates were significantly higher with ABBV-599 high dose compared with placebo at week 24 ($P$=0.021) and upadacitinib 30 mg compared with placebo at week 48 ($P$=0.034). The elsubrutinib monotherapy and ABBV-599 low-dose arms were discontinued due to inadequate efficacy in treating systemic disease; therefore, cutaneous outcomes were not further evaluated in both groups. A greater proportion of patients achieved the primary endpoint (both Systemic Lupus Erythematosus Responder Index 4 (SRI-4) and glucocorticoid dose ≤10 mg QD at week 24) with upadacitinib (54.8%; $P$=0.028) and ABBV-599 high dose (48.5%; $P$=0.081) vs placebo (37.3%). The SRI-4, British Isles Lupus Assessment Group-Based Composite Lupus Assessment (BICLA), and Lupus Low Disease Activity State (LLDAS) responses were consistently higher with ABBV-599 high dose and upadacitinib 30 mg compared with placebo at weeks 24 and 48. The ABBV-599 high dose and upadacitinib 30 mg arms significantly improved the incidence of flares and time to first flare through week 48 compared with placebo ($P$<0.05).[15]

The incidence of treatment-emergent adverse events (TEAEs) was lower in the ABBV-599 high dose group (10.3%) than in the upadacitinib 30 mg (21.0%) or placebo (17.3%) groups. AEs in patients receiving ABBV-599 high dose and upadacitinib 30 mg included nonfatal strokes (not attributed to the study drugs) and an increased incidence of serious infections in patients with underlying risk factors for infection. There was also a higher incidence of herpes zoster infections in the ABBV-599 high dose and upadacitinib 30 mg groups than in the placebo group. There were three deaths unrelated to the study drugs.[15]

A subsequent long-term extension study following the 48-week RCT further evaluated the safety and efficacy of oral upadacitinib 30 mg alone or combined with elsubrutinib 60 mg QD (ABBV-599 high dose) over 104 weeks in 185 enrolled adults with SLE. The participants originally assigned to the placebo group were then given ABBV-599 high dose. The proportion of patients who achieved CLASI-50 increased from week 48 to 104 and was 100%, 88.9%, and 100% in the upadacitinib 30 mg, ABBV-599 high dose, and placebo to ABBV-599 high dose groups, respectively. In the upadacitinib 30 mg and ABBV-599 high dose groups, the proportion of patients achieving SRI-4, BICLA, and LLDAS responses was sustained through week 104. Daily glucocorticoid dose decreased from week 0 to week 104 in all treatment groups. The incidence of overall flares through week 104 was maintained in the upadacitinib 30 mg group and decreased in the ABBV-599 high dose and placebo to ABBV-599 high dose groups.[14]

Exposure-adjusted TEAEs were highest in the placebo to ABBV-599 high dose group compared with upadacitinib 30 mg and continuous ABBV-599 high dose groups. Exposure-adjusted serious AE rates were low across all groups, with no deaths. Only one of five serious infections (limb abscess) was considered possibly related to upadacitinib. Herpes zoster occurred across all groups, and one patient in the upadacitinib 30 mg group developed hypogammaglobulinemia.[14]

**Evobrutinib**

Evobrutinib is an oral, highly selective, central nervous system-penetrating, covalent BTK inhibitor.[12] In vitro data indicate that evobrutinib attenuates pro-inflammatory M1 macrophage differentiation and suppresses B cell activation, differentiation, polarization, and cytokine release.[16] The efficacy of evobrutinib has been evaluated in autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, and SLE.[17]

A 52-week multicenter, dose-ranging RCT evaluated the safety and efficacy of evobrutinib in 469 participants with autoantibody-positive SLE, assigned to either oral evobrutinib 25 mg QD, 75 mg QD, 50 mg twice daily (BD), or placebo. There were no statistically significant differences between evobrutinib groups and placebo in general SRI-4 response, SRI-4 response in the serologically active subpopulation, and SRI-6 response in the high disease activity (HDA) subpopulation at week 52. Compared with placebo, evobrutinib 75 mg QD showed a numerically longer time to first BILAG A flare, but the difference was not statistically significant. Despite reduced total B cell numbers, there were no clinically meaningful differences between evobrutinib and placebo in organ-specific disease activity, flare rate, quality of life, corticosteroid use, or serum markers (C3/C4 complement levels, IgG, IgM, IgA, and anti-double-stranded DNA) over 52 weeks.[12]

All doses of evobrutinib were well tolerated. The rates of reported TEAE were similar between treatment groups. The most common AEs included increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, and lipase, as well as lymphopenia, noncardiac chest pain, otitis media, and headache. Two patients in the HDA subgroup died, although only one death of a patient with bone marrow failure was attributed to the treatment. Overall, 121 (25.8%) participants who discontinued treatment were generally balanced across groups. Treatment was discontinued due to AEs such as increased ALT or AST (n=64), lack of efficacy (n=13), or loss to follow-up (n=9).[12]

**Fenebrutinib**

Fenebrutinib is an oral, highly selective, reversible, and noncovalent BTK inhibitor that has demonstrated efficacy

in multiple sclerosis, rheumatoid arthritis, and chronic spontaneous urticaria.[18]

In a phase II multicenter RCT, 260 patients received oral fenebrutinib 150 mg QD, fenebrutinib 200 mg BD, or placebo for 48 weeks. SRI-4 response rates were slightly higher for fenebrutinib 150 mg QD and fenebrutinib 200 mg BD groups (51% and 52%, respectively) compared with placebo (44%), without between-group statistical significance. BICLA response rates were 53% with fenebrutinib 150 mg QD ($P$=0.086 vs placebo), 42% with fenebrutinib 200 mg BD ($P$=0.0879 vs placebo), and 41% with placebo. There were also no differences between treatment groups for time to flare. Relative to placebo, fenebrutinib was associated with reductions in anti-double-stranded DNA autoantibodies, BTK-dependent plasmablast RNA signature, total IgG, and IgM, along with increased C4 levels.[18]

More patients in the fenebrutinib 200 mg BD group reported serious AEs and experienced AEs that led to treatment withdrawal than the fenebrutinib 150 mg QD and placebo groups. One death occurred in the fenebrutinib 150 mg QD treatment group due to salivary gland neoplasm. The treatment groups developed similar rates of infection and serious infection. More patients in the fenebrutinib 200 mg BD group also experienced elevations in AST and ALT levels than the other arms.[18]

**Orelabrutinib**

Orelabrutinib is an oral, highly selective, and irreversible BTK inhibitor.[19] Orelabrutinib has demonstrated promise in B-cell malignancies, including mantle cell lymphoma and chronic lymphocytic leukemia, as well as autoimmune diseases such as multiple sclerosis and SLE.[19]

A 12-week multicenter phase Ib/IIa RCT evaluated oral orelabrutinib 50 mg, 80 mg, or 100 mg compared with placebo in 60 patients with active SLE. At week 12, SRI-4 response rates were 50%, 62%, and 64% with orelabrutinib 50 mg, 80 mg, and 100 mg, respectively, vs 36% with placebo. In the subgroup of participants with baseline Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) >8, SRI-4 responses were significantly higher with orelabrutinib 50 mg (80%, $P$=0.048), 80 mg (83%, $P$=0.048), and 100 mg (100%, $P$=0.029) in comparison with placebo (0%). Rash remission rates based on SLEDAI-2K were 40%, 75%, and 36% with orelabrutinib 50 mg, 80 mg, and 100 mg, respectively, versus 33% with placebo.[19]

Most AEs were mild to moderate. Among the 6 serious AEs reported, 3 were considered treatment related. At least 1 TEAE occurred in 80%, 93%, and 100% of patients receiving orelabrutinib 50 mg, 80 mg, and 100 mg, respectively, compared with 86% of patients taking the placebo. AEs included upper respiratory tract infection, decreased lymphocyte count, anemia, and abnormal liver function. No deaths occurred, and AE-related treatment discontinuation was infrequent.[19]

**Integrated Interpretation**

Despite the variable efficacy of BTK inhibitors in randomized SLE trials, preliminary favorable signals of cutaneous improvement with BTK inhibition support dedicated future clinical investigation in CLE. The RCT data demonstrated that elsubrutinib-based therapy (particularly ABBV-599 high dose) achieved significantly higher CLASI-50 response rates than placebo in patients with active skin disease, with durable cutaneous responses in long-term extension follow-up. Although upadacitinib 30 mg also achieved significantly higher CLASI-50 response rates than placebo, the high-dose ABBV-599 group achieved this endpoint in half the time. Orelabrutinib also showed consistently higher rates of rash remission than placebo across all doses.

Murine lupus models have demonstrated that BTK inhibition reduces disease activity and modulates immune signaling across key cell populations, including B cells, monocytes, and macrophages.[20] Murine studies also implicate B-cell hyperactivity and pathologically amplified B-cell receptor signaling in SLE pathogenesis and associated cutaneous disease.[21] Treatment with the selective BTK inhibitor BI-BTK-1 in MRL-lpr/lpr mice decreased macroscopic and microscopic skin lesions, cutaneous cellular infiltration, and inflammatory cytokine expression compared to controls in in vivo murine models.[21] These data suggest current SLE clinical trials investigating BTK inhibitors may incompletely capture clinically meaningful skin responses. To date, no clinical trials have evaluated BTK inhibitors in CLE. Given there are no FDA-approved treatments for CLE, dedicated CLE RCTs with BTK inhibitors could define safety and efficacy.

A strength of this systematic review is the inclusion of RCT data, providing high-level clinical evidence across BTK compounds and treatment durations. Interpretation is limited by the small number of available clinical trials, heterogeneity in endpoints, and variable reporting of skin-specific outcomes.

## CONCLUSION

BTK inhibition demonstrated mixed efficacy across SLE endpoints but showed potential for cutaneous benefit with elsubrutinib- and orelabrutinib-based regimens. The clinical findings are reinforced by murine model data showing attenuation of skin inflammation, reduced lesion burden, and modulation of B-cell pathways with BTK inhibition. These data suggest that current SLE studies may fail to fully capture skin-specific therapeutic effects. BTK inhibitors may be promising therapeutic options for cutaneous disease associated with SLE. Dedicated CLE-focused randomized controlled trials are needed to define safety, efficacy, optimal dosing, and durability of response.

## DISCLOSURES

All authors do not have any relevant conflicts of interest.

## REFERENCES

1. Justiz Vaillant AA, Goyal A, Varacallo MA. Systemic Lupus Erythematosus. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
2. Tian J, Zhang D, Yao X, et al. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis*. 2023;82(3):351-356. doi:10.1136/ard-2022-223035
3. Grand View Research I. Systemic lupus erythematosus (SLE) market size, share & trends analysis report by drug class, route of administration, distribution channel, region (2024–2030). 2025. GVR-2-68038-523-6. Available at: https://www.grandviewresearch.com/industry-analysis/systemic-lupus-erythematosus-sle-market.
4. Izmirly PM, Parton H, Wang L, et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol*. 2021;73(6):991-996. doi:10.1002/art.41632
5. Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review. *JAMA*. 2024;331(17):1480-1491. doi:10.1001/jama.2024.2315
6. Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. *Best Pract Res Clin Rheumatol*. 2013;27(3):391-404. doi:10.1016/j.berh.2013.07.008
7. Stokkermans TJ, Falkowitz DM, Trichonas G. Chloroquine and hydroxychloroquine toxicity. *StatPearls*. StatPearls Publishing; 2024.
8. Nashi E, Wang Y, Diamond B. The role of B cells in lupus pathogenesis. *Int J Biochem Cell Biol*. 2010;42(4):543-550. doi:10.1016/j.biocel.2009.10.011
9. Vale E, Garcia LC. Cutaneous lupus erythematosus: a review of etiopathogenic, clinical, diagnostic and therapeutic aspects. *An Bras Dermatol*. 2023;98(3):355-372. doi:10.1016/j.abd.2022.09.005
10. Lorenzo-Vizcaya A, Fasano S, Isenberg DA. Bruton's tyrosine kinase inhibitors: a new therapeutic target for the treatment of SLE? *Immunotargets Ther*. 2020;9:105-110. doi:10.2147/itt.S240874
11. Kong W, Deng W, Sun Y, et al. Increased expression of Bruton's tyrosine kinase in peripheral blood is associated with lupus nephritis. *Clin Rheumatol*. 2018;37(1):43-49. doi:10.1007/s10067-017-3717-3
12. Wallace DJ, Dörner T, Pisetsky DS, et al. Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled dose-ranging trial. *ACR Open Rheumatol*. 2023;5(1):38-48. doi:10.1002/acr2.11511
13. Fleischmann R, Friedman A, Drescher E, et al. Safety and efficacy of elsubrutinib or upadacitinib alone or in combination (ABBV-599) in patients with rheumatoid arthritis and inadequate response or intolerance to biological therapies: a multicentre, double-blind, randomised, controlled, phase 2 trial. *Lancet Rheumatol*. 2022;4(6):e395-e406. doi:10.1016/s2665-9913(22)00092-3
14. Merrill JT, Saxena A, Aringer M, et al. Efficacy and safety of upadacitinib as monotherapy or combined with elsubrutinib for the treatment of systemic lupus erythematosus: results through 104 weeks in a long-term extension study. *RMD Open*. 2025;11(3). doi:10.1136/rmdopen-2025-005742
15. Merrill JT, Tanaka Y, D'Cruz D, et al. Efficacy and safety of upadacitinib or elsubrutinib alone or in combination for patients with systemic lupus erythematosus: a phase 2 randomized controlled trial. *Arthritis Rheumatol*. 2024;76(10):1518-1529. doi:10.1002/art.42926
16. Montalban X, Arnold DL, Weber MS, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. *N Engl J Med*. 2019;380(25):2406-2417. doi:10.1056/NEJMoa1901981
17. Haselmayer P, Camps M, Liu-Bujalski L, et al. Efficacy and pharmacodynamic modeling of the BTK inhibitor evobrutinib in autoimmune disease models. *J Immunol*. 2019;202(10):2888-2906. doi:10.4049/jimmunol.1800583
18. Isenberg D, Furie R, Jones NS, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2021;73(10):1835-1846. doi:10.1002/art.41811
19. Li X, Li R, Zhu X, et al. Orelabrutinib, an irreversible inhibitor of Bruton's tyrosine kinase, for the treatment of systemic lupus erythematosus: a randomised, double-blind, placebo-controlled, phase Ib/IIa study. *Research Square*. 2025;PREPRINT (Version 1). doi:10.21203/rs.3.rs-7058001/v1
20. Mina-Osorio P, LaStant J, Keirstead N, et al. Suppression of glomerulonephritis in lupus-prone NZB × NZW mice by RN486, a selective inhibitor of Bruton's tyrosine kinase. *Arthritis Rheum*. 2013;65(9):2380-2391. doi:10.1002/art.38047
21. Chalmers SA, Wen J, Doerner J, et al. Highly selective inhibition of Bruton's tyrosine kinase attenuates skin and brain disease in murine lupus. *Arthritis Res Ther*. 2018;20(1):10. doi:10.1186/s13075-017-1500-0

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ORIGINAL ARTICLE

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# Immunosuppressive and Immunomodulatory Dermatologic Therapies: Cancer Risk for Patients With Active or Prior Malignancy

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## ABSTRACT

**Background:** The use of immunosuppressive and immunomodulatory medications in dermatology remains challenging in patients with active or prior malignancy due to concerns of cancer risk. Clinical trials have historically excluded this population, and real-world carcinogenesis requires prolonged follow-up, leaving dermatologists with limited guidance.

**Objective:** To review current evidence on malignancy risk associated with immunosuppressive and immunomodulatory agents in dermatologic disease, to provide considerations for patients with active or prior malignancy.

**Methods:** A narrative review was conducted to evaluate oncologic risk of major drug classes used in chronic inflammatory skin diseases, including biologics, methotrexate, calcineurin inhibitors, JAK inhibitors, acitretin, apremilast, and dupilumab.

**Results:** Broad immunosuppressants, including TNF-α inhibitors, methotrexate, and systemic calcineurin inhibitors, demonstrate increased malignancy risk. Targeted therapies, such as IL-12/17/23 inhibitors, apremilast, and dupilumab, are favorable, with no clear increased malignancy risk. Acitretin is non-immunosuppressive and chemoprotective against certain skin cancers. JAK inhibitors have limited dermatologic data suggesting malignancy risk but carry an FDA black box warning due to increased malignancy risk in rheumatoid arthritis.

**Conclusion:** Current evidence supports using therapies with lower oncologic risk and avoiding those with carcinogenic potential or using them cautiously with increased surveillance. Continued long-term, real-world studies are needed to further understand risks in this population and guide treatment.

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## INTRODUCTION

Immunosuppressive and immunomodulatory medications are widely utilized in dermatology to treat chronic inflammatory skin conditions. However, their use in patients with active or prior malignancy remains an area of uncertainty. Certain immunosuppressive medications have been linked to an increased incidence and mortality from melanoma and non-melanoma skin cancer (NMSC), and may contribute to recurrence of primary malignancies.[1] Clinical trials have historically excluded patients with malignancy, and carcinogenesis often requires prolonged follow-up, leaving limited evidence to guide treatment decisions.[2,3] Therefore, dermatologists may hesitate to initiate or continue systemic immunosuppressive therapy in this population. This article reviews current literature regarding the use and safety of immunosuppressive and immunomodulatory medications in this population. Table 1 summarizes key evidence on malignancy risk for each therapeutic class with odds ratios and confidence intervals when available.

### Biologics: Tumor Necrosis Factor Alpha Inhibitors

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine. Elevated levels are characteristic of several inflammatory skin diseases, due to keratinocyte proliferation, immune cell activation, and adhesion molecule upregulation.[4] TNF-α inhibitors (TNFis), including infliximab, adalimumab, etanercept, and certolizumab pegol, are FDA-approved for psoriasis, and adalimumab is approved for hidradenitis suppurativa.[5] Off-label uses include pemphigus vulgaris and pyoderma gangrenosum.[5]

TNFis have been associated with an increased cancer risk in psoriasis. Nested case-control analyses in the PSOLAR study (n=1260) found long-term (>12 months) TNFi therapy was associated with increased malignancy risk, excluding NMSC (odds ratio (OR), 1.54; 95% CI, 1.10–2.15).[6] However, in analyses restricted to monotherapy, this association was no longer statistically significant (OR, 1.29; 95% CI, 0.84–1.98).[6] A Korean study of 191,678 patients with psoriasis found overall cancer

**TABLE 1.**

**Summary of Key Studies Assessing Malignancy Risk With Immunosuppressive and Immunomodulatory Therapies in Dermatologic Disease**

| Therapeutic Class | Key Trials/ Studies | Study Design | Sample Size | Follow-up Time | Malignancy Risk (incidence ratio per 100 patient-years) | Malignancy Risk (other statistical measures with 95% CI) |
|---|---|---|---|---|---|---|
| TNF-α inhibitors/ TNFi | PSOLAR registry (TNFi, methotrexate)[6] | Nested case-control analysis within prospective registry | n=1260 (in analysis) | >0 months to ≥12 months | 0.55 (all treatments; excludes NMSC) | Adjusted OR:<br>2.05 [0.82–5.12] for >0 months to <3 months;<br>1.15 [0.63–2.09] for ≥3 months to <12 months<br>(OR, 1.54; 1.10–2.15; *P*=.01) for ≥12 months |
| | Korean nationwide cohort study (TNFi, IL12/23i)[7] | Retrospective population-based cohort | n=191678 | >1 year | 0.60 (all treatments) | aHR, 1.41, (1.01–1.97) |
| IL-12, IL-23, IL-17 inhibitors | International population-based study (IL-17i/IL-23i vs TNFi)[9] | Retrospective population-based cohort | n= 15331 (IL-17i), n=5832 (IL-23i) | 5 years | NR | Overall risk decreased across several cancers:<br>IL-23i NHL (HR, 0.39; 0.19–0.78; *P*=0.006),<br>IL-17i NHL (HR, 0.58; 0.40–0.82; *P*=0.002), |
| | Ustekinumab phase II/ phase III trials[12] | Pooled analysis of randomized phase II/III trials | n=3117 | Up to 3 years | 1.30 (adjusted for duration of follow-up) | NR |
| | VOYAGE 1 and 2 trials (guselkumab)[11] | Randomized phase III trials | n=1221 | 156 weeks | 0.28 (NMSC), 0.47 (other cancers) | NR |
| Methotrexate | Danish nationwide case-control study[15] | Case-control | n=176176 (cases) | Minimum 2.7 years | NR | Adjusted OR:<br>1.29 (1.20–1.38) for basal cell carcinoma<br>1.61 (1.37–1.89) for cutaneous squamous cell carcinoma<br>1.35 (1.13–1.61) for cutaneous malignant melanoma |
| | PSOLAR registry (TNFi, methotrexate)[6] | Nested case-control analysis within prospective registry | n=1260 (in analysis) | >0 months to ≥12 months | 0.55 (all treatments; excludes NMSC) | Adjusted OR:<br>1.30 [0.34–5.01] for >0 months to <3 months<br>1.01[0.45–2.28] for ≥3 months to <12 months<br>.98 [0.63–1.54] for ≥12 months) |
| Calcineurin Inhibitors | Multi-national cohort study (cyclosporine)[22] | Retrospective cohort | n=1252 | 5 years | 1.08 | NR |
| | Korean cohort study (topical tacrolimus and pimecrolimus)[24] | Multi-center Retrospective cohort | n=25694 | 38 months (median) | 0.0136 (lymphoma), 0.017 (NMSC), 0.0052 (melanoma) | NR |
| JAK inhibitors | Measure Up 1 and 2 phase III trials (upadacitinib)[27] | Pooled analysis of randomized phase III trials | n=1608 | 52 weeks | 0.6 (15 mg dose), 0.9 (30 mg dose) | NR |
| | ORAL Surveillance (tofacitinib)[29] | Prospective phase IIIb-IV safety trial | n=2911 | 4 years (median) | NR | HR 1.33 (1.04–2.09) |
| Acitretin | North Central Cancer Treatment Group Study 969251[34] | Prospective randomized controlled trial | n=70 | 2 years | NR | Rate of new primary NMSC: OR 0.41 (0.15–1.13), *P*=.13 |
| Apremilast | International clinical trials[37] | Pooled analysis of 15 randomized controlled trials (open-label extension phases) | n=4183 | Up to 5 years | 1.0 | NR |
| Dupilumab | American cohort study[42] | Retrospective cohort | n=9707, 1627 on dupilumab | 5 years | 1.29 (primary malignancy); 0.80 (NMSC); 0.092 (recurrent malignancy) | NR |

aHR, adjusted hazard ratio; HR, hazard ratio; NR, not reported; NMSC, non-melanoma skin cancer; NHL, Non-Hodgkin Lymphoma; OR, odds ratio; SIR, standardized incidence ratio

risk was elevated with TNFi use (adjusted hazard ratio (aHR), 1.41; 95% CI, 1.01–1.97), specifically for Non-Hodgkin lymphoma (NHL; aHR, 2.98; 95% CI, 1.02–8.69), but not other cancers including NMSC.[7]

Oncologic risk with TNF is complex and influenced by factors including personal malignancy history, treatment duration, and concomitant immunosuppressant use.[6] Certain malignancies appear to be more strongly linked to TNFi therapy, such as NHL. These studies suggest that although there is evidence of increased risk of malignancy with TNFis, they can be safely used in patients with past malignancy, given close follow-up for new or recurrent malignancy.

**Biologics: Interleukin Inhibitors**

Interleukins, specifically IL-12/17/23 cytokines, play key roles in the pathogenesis of immune-mediated skin diseases, particularly psoriasis. IL-12 and IL-23 promote differentiation of Th1 and Th17 cells, respectively, which in turn secrete a pro-inflammatory cytokine cascade.[8] With high efficacy and favorable side effect profiles, these agents are first-line biologics in moderate-to-severe psoriasis, and off-label uses include pyoderma gangrenosum and systemic lupus erythematosus.[5,8]

Limited data exist on cancer risk with the use of these biologics, but it currently suggests no increased risk. A population-based cohort study comparing TNFi versus IL-17i and IL-23i in patients with psoriasis found patients receiving the interleukin inhibitors had a decreased risk of up to 26 identified malignancies, including melanoma and NMSC.[9] In a pooled safety analysis of phase II and III trials, patients treated for psoriasis with the IL-12/23i ustekinumab (n=3117) had no increased risk of malignancy (excluding NMSC) compared with the general population.[10] The VOYAGE 1 and 2 trials (n=1221) assessing safety of the IL-23i guselkumab found an incidence of 0.28 per 100 patient-years for NMSC (95% CI, 0.13–0.53) and 0.47 per 100 patient-years for other cancers (95% CI, 0.26–0.77) over a 156-week period.[11]

Overall, current evidence suggests interleukin inhibitors can be safe for patients in whom malignancy is a concern.

**Methotrexate**

Methotrexate is an anti-folate drug with anti-proliferative and anti-inflammatory effects. It limits epithelial cell hyperplasia and suppresses pro-inflammatory cytokine production, including TNF-α.[12,13] Methotrexate is approved for severe psoriasis but is used off-label for other dermatologic diseases, particularly atopic dermatitis (AD).[14]

Data on cancer risk with methotrexate use is inconclusive, with some studies suggesting increased malignancy risk and others suggesting no significant association. A Danish case-control study including almost 2,000,000 participants found an increased risk of basal cell carcinoma (BCC; OR, 1.45; 95% CI, 1.37–1.54), cutaneous squamous cell carcinoma (cSCC; OR, 1.61; 95% CI, 1.37–1.89), and cutaneous malignant melanoma (CMM; OR, 1.35; 95% CI, 1.13–1.61), with risk increasing at higher cumulative doses.[15] This risk was no longer statistically significant when restricted to patients taking methotrexate for psoriasis.[15] Similarly, the PSOLAR study found no elevated risk of malignancy (excluding NMSC) in patients on methotrexate for psoriasis, even with long-term therapy (≥12 months).[6] In contrast, a systematic review and meta-analysis of 11,875 patients with psoriasis, including 2,192 on methotrexate, found methotrexate increased the risk of developing NMSC by 2.8-fold (95% CI, 1.47–5.39; $P$=0.002).[16] Another systematic review and meta-analysis (n=16642) evaluating melanoma rates in low-dose methotrexate use across multiple conditions found a 15% increased melanoma risk (pooled relative risk (RR), 1.15; 95% CI, 1.08–1.22); however, the absolute risk increase was negligible considering the overall incidence of melanoma globally.[17]

Additional data are needed to better understand the long-term cancer risk of methotrexate for patients with prior or current malignancy. Currently, evidence suggests methotrexate is safe in patients with cancer history but should be used cautiously in those with significant skin cancer history, with emphasis on routine skin exams for surveillance.

**Calcineurin Inhibitors**

Calcineurin is a calcium- and calmodulin-dependent phosphatase that disrupts pro-inflammatory cytokine transcription, subsequently impairing proliferation and differentiation of CD4+ helper and CD8+ cytotoxic T-cells.[18] Topical calcineurin inhibitors (TCIs) are approved for moderate-to-severe AD with suboptimal response to standard treatments and are also first-line for localized vitiligo.[19] They have been used off-label in psoriasis and seborrheic dermatitis.[19] Cyclosporine, a systemic calcineurin inhibitor (CNI), is reserved for severe or refractory cases of psoriasis or AD.[20,21]

The carcinogenic potential of cyclosporine is well established. A 5-year cohort study of psoriasis patients on cyclosporine (n=1252) found that 3.8% of patients developed malignancies, 49% being skin cancers.[22] Notably, they report a 2.1-fold increased malignancy risk compared with the general population, driven by a 6-fold increased risk of NMSC, specifically cSCC.[22] TCIs do not carry the same risk. A systematic review and meta-analysis of cohort (n=408366) and case-control (n=3898) studies of TCI use in AD found no increased cancer risk.[23] However, an elevated RR of lymphoma was noted, with authors noting the absolute risk remained low, reflecting potential confounding or bias.[23] A retrospective cohort study of vitiligo patients (n=25694) treated with TCIs for ≥6 weeks found no increased risk of NMSC,

melanoma, or lymphoma in 95,203 person-years with median follow-up of <4 years, further supporting TCI safety.[24]

Overall, the literature suggests increased malignancy risk with cyclosporine. This risk burden is influenced by independent factors including exposure length (>2 years), prior PUVA (psoralen and ultraviolet A), and prior immunosuppressive therapy.[22] Accordingly, CNIs should be avoided in patients with active or prior malignancy or limited to short durations for acute flares.

**JAK Inhibitors**

Janus kinases are intracellular tyrosine kinases essential in cytokine-mediated signal transduction, regulating genes involved in immune cell proliferation, differentiation, and inflammatory responses.[25] Through signal disruption, JAK inhibitors (JAKi) are approved to treat several dermatologic conditions, including alopecia areata (AA), AD, and vitiligo.[26] Off-label uses include systemic lupus erythematosus and lichen planus.[26]

The literature evaluating malignancy risk with JAKi in dermatologic conditions is expanding, reflecting their relatively recent adoption in practice. Pooled data of two upadacitinib trials (n=1608) reported an exposure-adjusted event rate of malignant neoplasms of 0.6 and 0.9 per 100 patient-years for 15 and 30 mg doses, respectively.[27] NMSC was the most frequently reported malignancy across both treatment groups, with rare cases of breast, gastric, and anal cancer reported during the 52-week follow-up period.[27] In phase III AA trials, the incidence of malignancy during the 36-week follow-up period was comparable between 598 baricitinib-treated patients and placebo, with a single case of B-cell lymphoma in the baricitinib-treated group.[28] Patients were eligible for inclusion if they: (1) were aged ≥18 years; (2) had a dermatologist-confirmed diagnosis of PsO; (3) reported English as their primary language; (4) could read and write in English; and (5) were available for follow-up at 1 month.

Studies assessing patients treated with systemic JAKi for other inflammatory conditions strongly support an elevated malignancy risk. Notably, JAKi carry an FDA black box warning based on the ORAL Surveillance trial of tofacitinib in rheumatoid arthritis, in which tofacitinib-treated patients (n=2911) demonstrated malignancy compared with TNFi (4.2% vs 2.9%; HR, 1.48; 95% CI, 1.04–2.09) over a 4-year median follow-up period.[29] Overall, while current data do not strongly support increased malignancy risk with systemic JAKi in dermatologic disease, it remains insufficient.

**Acitretin**

Acitretin is a synthetic oral retinoid that exerts anti-inflammatory and anti-proliferative effects by inhibiting production of pro-inflammatory cytokine IL-6, reducing Th17 cell production and increasing T-regulatory cell production.[30] Acitretin, although largely replaced by biologics, is approved for psoriasis, and off-label uses include disorders of keratinization, such as Darier's disease.[31,32]

Unlike other systemic immunomodulators, acitretin has a unique oncologic safety profile. It has chemoprotective effects against NMSC, making it a good choice for patients who are immunosuppressed or at increased skin cancer risk.[31] A randomized controlled trial in renal transplant recipients (n=28) found decreased incidence of cSCC in 3 years on low-dose acitretin, with rates rising upon discontinuation.[33] In a prospective, randomized controlled trial of 70 patients with NMSC history, acitretin showed a trend towards reduced incidence of new NMSC.[34]

The data suggest acitretin is safe for patients with current or prior malignancy and may offer protective benefit in high-risk patients against development of new skin cancers.

**Apremilast**

Apremilast is an oral small-molecule inhibitor that modulates inflammation by inhibiting pro-inflammatory cytokines including TNF-α and IFN-γ, and upregulating anti-inflammatory cytokines like IL-10.[35] It is approved for psoriasis, psoriatic arthritis, and oral ulcers of Behçet's disease.[36]

Current literature does not demonstrate an association between apremilast and increased malignancy risk. A pooled analysis of 15 randomized, placebo-controlled studies with 4,183 patients with up to 5 years of apremilast exposure found the incidence of malignancy to be 1.0 per 100 patient-years, with no new safety signals noted.[37] One systematic review evaluated psoriasis patients on apremilast with comorbid serious disease and found only 3 cases of cancer progression out of 456 patients with active or prior malignancy.[38] A survey of dermatologists (n=57) found apremilast was the most prescribed medication for patients with psoriasis and concomitant malignancy, highlighting clinician comfort.[39]

Taken together, apremilast represents a suitable option when malignancy is a concern. However, continued long-term follow-up studies are needed to clarify safety in diverse patient populations.

**Dupilumab**

Dupilumab is a fully human monoclonal antibody that inhibits signaling of IL-4 and IL-13, cytokines critical to Th2-mediated inflammation, epidermal permeability, and impaired skin barrier function.[40] Dupilumab is approved to treat moderate-to-severe AD and bullous pemphigoid.[41]

Dupilumab does not have a well-established association with cancer in dermatologic treatment. A 5-year retrospective study of 9,707 patients with AD, including 1,627 on dupilumab, found no increased risk of new primary cancers on dupilumab (aHR, 1.010; *P*=.946) and no increased risk of cancer recurrence on dupilumab (aHR, 0.828; *P*=.758).[42] Another study of 139 patients with AD and concurrent hematologic disease (including malignancy) found no evidence of cancer progression during dupilumab therapy with a median follow-up of 52 weeks.[43] Dupilumab is currently recommended as first-line treatment for AD in patients with a history of malignancy.[44]

Conversely, some studies have shown an association between dupilumab and cutaneous T-cell lymphoma (CTCL) risk; however, it is unclear if this represents early CTCL cases misdiagnosed as AD or true malignant transformation due to dupilumab.[45] Therefore, dupilumab should be used cautiously in atypical AD presentations in older adults.

## CONCLUSION

Overall, literature supports prioritizing immunosuppressive and immunomodulatory agents with narrower targets and lower oncologic risk and avoiding agents with clear carcinogenic potential. As long-term, real-world evidence grows, dermatologists should balance disease control with individualized cancer risk rather than broadly withholding these therapies in patients with active or prior malignancy.

## DISCLOSURES

Dr Dulmage is a consultant for Novocure and serves on the Data Safety and Management Board of Hoth Therapeutics. The other authors have no conflicts of interest to disclose.

## REFERENCES

1. Griffith CF. Skin cancer in immunosuppressed patients. *JAAPA.* 2022;35(2):19-27. doi:10.1097/01.JAA.0000805800.77311.4c
2. Patel RR, Parisi R, Verma V, et al. Association between prior malignancy exclusion criteria and age disparities in cancer clinical trials. *Cancers (Basel).* 2022;14(4):1048. doi:10.3390/cancers14041048
3. Kempen JH, Gangaputra S, Daniel E, et al. Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. *Am J Ophthalmol.* 2008;146(6):802-812.e1. doi:10.1016/j.ajo.2008.04.035
4. Ovcina-Kurtovic N, Kasumagic-Halilovic E. Serum levels of tumor necrosis factor - alpha in patients with psoriasis. *Mater Sociomed.* 2022;34(1):40-43. doi:10.5455/msm.2022.33.40-43
5. Hong JJ, Hadeler EK, Mosca ML, et al. Off-label uses of TNF-a inhibitors and IL-12/23 inhibitors in dermatology. *Dermatol Online J.*
6. Fiorentino D, Ho V, Lebwohl MG, et al. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. *J Am Acad Dermatol.* 2017;77(5):845-854.e5. doi:10.1016/j.jaad.2017.07.013
7. Jung JM, Kim YJ, Chang SE, et al. Cancer risks in patients with psoriasis administered biologic therapy: a nationwide population-based study. *J Cancer Res Clin Oncol.* 2023;149(19):17093-17102. doi:10.1007/s00432-023-05387-6
8. Poizeau F, Leducq S, Fardet L, et al. Treatment of moderate-to-severe psoriasis in adults: an expert consensus statement using a Delphi method to produce a decision-making algorithm. *Ann Dermatol Venereol.* 2024;151(3):103287.
9. Kridin K, Abdelghaffar M, Mruwat N, et al. Are interleukin 17 and interleukin 23 inhibitors associated with malignancies?-Insights from an international population-based study. *J Eur Acad Dermatol Venereol.* 2024;38(2):315-324. doi:10.1111/jdv.19520
10. Gordon KB, Papp KA, Langley RG, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol.* 2012;66(5):742-751. doi:10.1016/j.jaad.2011.06.041
11. Reich K, Griffiths CEM, Gordon KB, et al. Maintenance of clinical response and consistent safety profile with up to 3 years of continuous treatment with guselkumab: results from the VOYAGE 1 and VOYAGE 2 trials. *J Am Acad Dermatol.* 2020;82(4):936-945. doi:10.1016/j.jaad.2019.11.040
12. Czarnecka-Operacz M, Sadowska-Przytocka A. The possibilities and principles of methotrexate treatment of psoriasis - the updated knowledge. *Postepy Dermatol Alergol.* 2014;31(6):392-400. doi:10.5114/pdia.2014.47121
13. Festugato M. Adenosine: an endogenous mediator in the pathogenesis of psoriasis. *An Bras Dermatol.* 2015;90(6):862-867. doi:10.1590/abd1806-4841.2015368
14. Mocanu M, Procopciuc D, Gheucă-Solovăstru DF, et al. An overview of methotrexate indications in skin diseases. *Medicina (Kaunas).* 2024;60(7):1024. doi:10.3390/medicina60071024
15. Polesie S, Gillstedt M, Schmidt SAJ, et al. Use of methotrexate and risk of skin cancer: a nationwide case-control study. *Br J Cancer.* 2023;128(7):1311-1319. doi:10.1038/s41416-023-02172-7
16. Lang Houser ME, Stewart JR, Brewer JD. Psoriasis patients treated with methotrexate have an increased risk of nonmelanoma skin cancer: a systematic review and meta-analysis. *Cureus.* 2023;15(4):e37174. doi:10.7759/cureus.37174
17. Yan MK, Wang C, Wolfe R, et al. Association between low-dose methotrexate exposure and melanoma: a systematic review and meta-analysis. *JAMA Dermatol.* 2022;158(10):1157-1166. doi:10.1001/jamadermatol.2022.3337
18. Gutfreund K, Bienias W, Szewczyk A, et al. Topical calcineurin inhibitors in dermatology. Part I: properties, method and effectiveness of drug use. *Postepy Dermatol Alergol.* 2013;30(3):165-169. doi:10.5114/pdia.2013.35619
19. Guenther L, Lynde C, Poulin Y. Off-label use of topical calcineurin inhibitors in dermatologic disorders. *J Cutan Med Surg.* 2019;23(4_suppl):27S-34S. doi:10.1177/1203475419857668
20. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol.* 2020;82(6):1445-1486. doi:10.1016/j.jaad.2020.02.044
21. AAAAI/ACAAI JTF Atopic Dermatitis Guideline Panel, Chu DK, Schneider L, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol.* 2024;132(3):274-312. doi:10.1016/j.anai.2023.11.009
22. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol.* 2003;120(2):211-216. doi:10.1046/j.1523-1747.2003.12040.x
23. Lam M, Zhu JW, Tadrous M, et al. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. *JAMA Dermatol.* 2021;157(5):549-558. doi:10.1001/jamadermatol.2021.0345
24. Ju HJ, Han JH, Kim MS, et al. The long-term risk of lymphoma and skin cancer did not increase after topical calcineurin inhibitor use and phototherapy in a cohort of 25,694 patients with vitiligo. *J Am Acad Dermatol* 2021;84(6):1619-1627. doi:10.1016/j.jaad.2021.01.067
25. Klein B, Treudler R, Simon JC. JAK-inhibitors in dermatology - small molecules, big impact? Overview of the mechanism of action, previous study results and potential adverse effects. *J Dtsch Dermatol Ges.* 2022;20(1):19-24. doi:10.1111/ddg.14668
26. Huang MY, Armstrong AW. Janus-kinase inhibitors in dermatology: a review of their use in psoriasis, vitiligo, systemic lupus erythematosus, hidradenitis suppurativa, dermatomyositis, lichen planus, lichen planopilaris, sarcoidosis and graft-versus-host disease. *Indian J Dermatol Venereol Leprol.* 2023;90(1):30-40. doi:10.25259/IJDVL_15_2023
27. Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the Measure Up 1 and Measure Up 2 randomized clinical trials. *JAMA Dermatol.* 2022;158(4):404-413. doi:10.1001/jamadermatol.2022.0029
28. King B, Ohyama M, Kwon O, et al. Two phase 3 trials of baricitinib for alopecia areata. *N Engl J Med.* 2022;386(18):1687-1699. doi:10.1056/NEJMoa2110343
29. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med.* 2022;386(4):316-326. doi:10.1056/NEJMoa2109927
30. Zito PM, Patel P, Mazzoni T. Acitretin. In: *StatPearls.* Treasure Island, FL: StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519571/

31. Booij MT, Van De Kerkhof PC. Acitretin revisited in the era of biologics. *J Dermatolog Treat.* 2011;22(2):86-89. doi:10.3109/09546630903578582
32. Sarkar R, Chugh S, Garg VK. Acitretin in dermatology. *Indian J Dermatol Venereol Leprol.* 2013;79(6):759-771. doi:10.4103/0378-6323.120721
33. Harwood CA, Leedham-Green M, Leigh IM, et al. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol.* 2005;141(4):456-464. doi:10.1001/archderm.141.4.456
34. Kadakia KC, Barton DL, Loprinzi CL, et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). *Cancer.* 2012;118(8):2128-2137. doi:10.1002/cncr.26374
35. Schett G, Sloan VS, Stevens RM, et al. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. *Ther Adv Musculoskelet Dis.* 2010;2(5):271-278. doi:10.1177/1759720X10381432
36. Padda IS, Bhatt R, Parmar M. Apremilast. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572078/
37. Mease PJ, Hatemi G, Paris M, et al. Apremilast long-term safety up to 5 years from 15 pooled randomized, placebo-controlled studies of psoriasis, psoriatic arthritis, and Behçet's syndrome. *Am J Clin Dermatol.* 2023;24(5):809-820. doi:10.1007/s40257-023-00783-7
38. Tsentemeidou A, Sotiriou E, Sideris N, et al. Apremilast in psoriasis patients with serious comorbidities: a case series and systematic review of literature. *Dermatol Pract Concept.* 2022;12(4):e2022179. doi:10.5826/dpc.1204a179
39. Bowe S, Murphy M, Bourke J, et al. Prescribing practices among psoriasis experts for patients with concomitant malignancy: a survey of International Psoriasis Council members. *Clin Exp Dermatol.* 2025;50(9):1818-1826. doi:10.1093/ced/llaf198
40. Gooderham MJ, Hong HC, Eshtiaghi P, et al. Dupilumab: a review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl 1):S28-S36. doi:10.1016/j.jaad.2017.12.022
41. Olbrich H, Sadik CD, Ludwig RJ, et al. Dupilumab in inflammatory skin diseases: a systematic review. *Biomolecules.* 2023;13(4):634. doi:10.3390/biom13040634
42. Owji S, Ungar B, Dubin DP, et al. No association between dupilumab use and short-term cancer development in atopic dermatitis patients. *J Allergy Clin Immunol Pract.* 2023;11(5):1548-1551. doi:10.1016/j.jaip.2022.12.018
43. Bettolini L, Bighetti S, Ferrucci SM, et al. Safety and effectiveness of dupilumab in atopic dermatitis patients with hematologic comorbidities: a multicenter, retrospective study. *Antibodies (Basel).* 2025;14(3):75. doi:10.3390/antib14030075
44. Drucker AM, Lam M, Flohr C, et al. Systemic therapy for atopic dermatitis in older adults and adults with comorbidities: a scoping review and International Eczema Council survey. *Dermatitis.* 2022;33(3):200-206. doi:10.1097/DER.0000000000000845
45. Hasan I, Parsons L, Duran S, et al. Dupilumab therapy for atopic dermatitis is associated with increased risk of cutaneous T cell lymphoma: a retrospective cohort study. *J Am Acad Dermatol.* 2024;91(2):255-258. doi:10.1016/j.jaad.2024.03.039

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SHOTS, SHOTS, SHOTS:
IS THERE SUCH A THING AS ONE TOO MANY?

Corticosteroid injections are everywhere in musculoskeletal medicine. Epidurals, joints, facets, bursae: when inflammation and pain are the targets, steroids have long been one of the sharpest tools in the shed. But does local treatment mean only local consequences? And when does another shot become one shot too many? In this episode of the JDD Podcast Corticosteroid Stewardship Series, host Dr. Adam Friedman sits down with Dr. Joseph Bax, an interventional physiatrist and Assistant Professor of Orthopedics and Rehabilitation and Human Performance at the Icahn School of Medicine at Mount Sinai, to inject some perspective into procedural corticosteroid use.

The two take aim at the when, where, why, and how often of corticosteroid injections: Who is the right patient? How much is too much? Perhaps most importantly, who is keeping the steroid scorecard when one patient gets an epidural from one physician, a joint injection from another, oral prednisone somewhere else, and a topical steroid from...well, you know who? From cumulative corticosteroid exposure and comorbidities to physical therapy, radiofrequency ablation, nerve blocks, PRP, and other steroid-sparing strategies, Drs. Friedman and Bax explore how to reduce reliance without replacing evidence-based medicine with wishful thinking. So before you say, "Just give 'em another shot," give this episode a gander. Good corticosteroid stewardship isn't about taking the needle away, it's about the right shot, right patient, right time, and right reason.



GUEST
Dr. Joseph Bax

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ORIGINAL ARTICLE

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# Evaluating the Clinical Efficacy, Utility, and Role of the 40-Gene Expression Profiling Test in Assessing Prognosis of Cutaneous Squamous Cell Carcinoma: An Expert Consensus Panel

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## ABSTRACT

**Background:** The 40-gene expression profiling (40-GEP) test has been validated to identify patients at highest risk for nodal or distant metastasis, as well as those most likely to benefit from adjuvant radiation therapy (ART). The purpose of this expert consensus panel was to review the published literature on the clinical efficacy, utility, and role of the 40-GEP test in providing prognostic information for high-risk cSCC.

**Methods:** A comprehensive literature search was completed using a combination of keywords "40-gene expression profiling," "cutaneous squamous cell carcinoma," "prognosis," "clinical efficacy," and "clinical utility". A panel of 8 dermatologists with significant expertise in management of cSCC gathered to review the articles and create consensus statements. A modified Delphi process was used to approve each statement, and a strength of recommendation was assigned.

**Results:** The literature search produced 55 articles. Screening resulted in 18 articles that met criteria. The panel unanimously voted to adopt 8 consensus statements and recommendations: 5 with strength "A", 2 with strength "B", and 1 with strength "C".

**Conclusion:** The 40-GEP test augments staging accuracy by improving metastatic and local recurrence risk stratification beyond traditional staging systems. It also has clinical utility in informing decisions regarding adjuvant radiation therapy and guiding broader management strategies.

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## INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most prevalent skin cancer, and its incidence and prevalence are rising.[1,2] Traditional treatment methods include surgical interventions (ie, wide local excision and Mohs micrographic surgery), though for select patients other interventions may be more appropriate or required (ie, radiation therapy, immunotherapy).[3] cSCC has the potential to develop into metastatic disease, with approximately 4% of patients experiencing locoregional or distant recurrence and may lead to death.[4-6] Therefore, patients with higher risk of poor outcomes from cSCC may benefit from more intensive management.

Identifying those at risk of recurrence and metastasis has been based on several staging systems available for cSCC, which include the American Joint Committee on Cancer 8th edition (AJCC8) and the Brigham and Women's Hospital (BWH) staging system. The National Comprehensive Cancer Network (NCCN) is a guideline framework incorporating staging systems that provides risk stratification for cSCC. Each of these systems has a distinctive method of classifying cSCC as high-risk, which is based on a combination of various clinicopathologic features.[7-10] Given the differences in these approaches, there remains a lack of uniformity for the classification and management of high-risk cSCCs following surgical excision with clear margins.[10-12]

The 40-gene expression profile (GEP) test analyzes formalin-fixed paraffin-embedded, primary cSCC tissue to stratify tumors into low (Class 1), high (Class 2A), and highest (Class 2B) risk for regional or distant metastasis.[13-18] It has been validated in multiple studies to identify patients at highest risk for nodal or distant metastasis independent of existing risk assessment tools, as well as those most likely to benefit from adjuvant radiation therapy (ART).[13-21] Although substantial data are available, few guidelines outline how and when to integrate this test into clinical practice.

The purpose of this expert consensus panel was to review the published literature on the clinical efficacy, utility, and role of the 40-GEP test in providing prognostic information for high-risk cSCC, in order to guide clinical decision-making and enhance patient care.

## MATERIALS AND METHODS

### Literature Search and Study Selection

A comprehensive literature search of PubMed/Scopus/Google Scholar was completed on August 13th, 2025, using a combination of keywords "40-gene expression profiling," "cutaneous squamous cell carcinoma," "prognosis," "clinical efficacy," and "clinical utility," along with the Boolean term "AND" for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. This study did not require IRB approval. Articles were screened for relevance to the topic of 40-GEP testing for providing prognostic information for cSCC. Eight experts with expertise in the management of cSCC were asked to participate in a panel. The articles that met inclusion criteria were distributed to the panelists, and each member assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[22] These levels include level 1 (good-quality, patient-oriented evidence), level 2 (limited-quality, patient-oriented evidence), or level 3 (other).[22]
Development of Consensus Statements

The panel convened on October 22nd, 2025, to discuss the studies and create consensus statements. A modified Delphi process was utilized to reach consensus for each statement,[22] which requires a supermajority approval (6 out of 8) for adoption of a recommendation through multiple rounds of real-time voting. This is a frequently utilized method to develop expert recommendations in dermatology.[23-27] Consensus statements were assigned a strength of recommendation of A (consistent, good-quality, patient-oriented evidence), B (inconsistent, limited-quality, patient-oriented evidence), or C (consensus, opinion, etc).

## RESULTS

### Literature Search and Study Selection

The literature search resulted in 55 articles that met search criteria. After a comprehensive screening process, 18 articles were selected as relevant to the research questions.

### Levels of Evidence Designation

For the 18 articles that were evaluated, the panel assigned level 1 evidence to 1 article, level 2 evidence to 9 articles, and level 3 evidence to 7 articles (Table 1).

### Consensus Statements

The panel developed 8 consensus statements. Of the 8 statements, all received a unanimous (8/8) vote for adoption. Each statement was assigned a strength based on SORT criteria (Table 2).

***Statement 1:*** *The 40-GEP test provides statistically significant and clinically meaningful enhancement of the 3-year metastatic risk assessment of high-risk cSCC beyond traditional staging systems (AJCC8, BWH). (SORT Level A)*

The 40-GEP test has consistently demonstrated significant prognostic value.[13-15,28] A systematic review and meta-analysis found that overall 3-year metastasis-free survival rates were 92.4% for Class 1, 78.9% for Class 2A, and 45.4% for Class 2B, indicating a significant difference in the risk classification of each 40-GEP group.[28] Other studies have also reported significant differences ($P$<0.0001) in the metastatic risk profiles of the 40-GEP results.[13,15] When integrated with clinicopathologic risk factors, metastasis rates were near the general cSCC population for 40-GEP Class 1 and were ≥50% for Class 2B, regardless of the number of risk factors.[14] Multivariate modeling demonstrates that the 40-GEP test provides independent and additive prognostic value to the AJCC8 and BWH staging systems.[14] One study reported 77.8% sensitivity of a Class 2 result, 55.5% specificity of Class 2 result, 23.6% positive predictive value of Class 2 result, and a 96.9% specificity of Class 2B, which was greater than those for high-stage AJCC8 (sensitivity 38.1%, specificity 84.3%)and BWH tumors (sensitivity 30.2%, specificity 89.6%).[14] Additionally, pooled analyses revealed the positive predictive value was significantly greater in Class 2B (55.9%) compared with AJCC8 (33%) or BWH (29%).[28] Combining 40-GEP Class 2B results with current staging systems results in ≥3-fold improvement in metastasis prediction compared with them alone[AJCC8:hazard ratio (HR) 9.98 vs 2.61; BWH: HR 8.62 vs 2.18].[28]

***Statement 2:*** *Data suggest that the 40-GEP test enhances local recurrence risk assessment of NCCN high-risk cSCC beyond traditional staging systems (AJCC8, BWH). (SORT Level B)*

The NCCN high-risk cSCC group poses treatment challenges, as >30% of local recurrence (LR)or metastases occur in this group.[29,30] AJCC8 and BWH staging do not reliably identify greater risk of LR or metastasis in the NCCN high-risk cSCC group.[30] On the other hand, evidence shows that the LR rate for 40-GEP Class 2B (28.6%)and Class 2A (14.5%)is greater than that of Class 1 (5.8%) ($P$=0.003).[30] In a multivariable analysis, 40-GEP results of Class 2A and 2B were the only significant predictors of

**TABLE 1.**

| SORT Criteria Level of Evidence for Articles | |
|---|---|
| **Article** | **Level of Evidence** |
| Association of a 40-gene expression profile with risk of metastatic disease progression of cutaneous squamous cell carcinoma and specification of benefit of adjuvant radiation therapy. | 2 |
| Analytical validity of decisiondx-scc, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. | 3 |
| Integrating 40-gep testing to improve clinical recommendations for adjuvant radiation for cutaneous squamous cell carcinoma: multidisciplinary consensus guidelines. | 3 |
| Real-world evidence shows clinicians appropriately use the prognostic 40-gene expression profile (40-gep) test for high-risk cutaneous squamous cell carcinoma (cSCC) patients. | 3 |
| Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test. | 2 |
| Impact of a prognostic 40-gene expression profiling test on clinical management decisions for high-risk cutaneous squamous cell carcinoma. | 3 |
| The prognostic value and clinical utility of the 40-gene expression profile (40-gep) test in cutaneous squamous cell carcinoma: systematic review and meta-analysis. | 2 |
| Inconsistent associations between risk factor profiles and adjuvant radiation therapy (ART) treatment in patients with cutaneous squamous cell carcinoma and utility of the 40-gene expression profile to refine art guidance. | 2 |
| The 40-gene expression profile test identifies patients with national comprehensive cancer network high-risk cutaneous squamous cell carcinoma at high risk of poor outcomes to inform management decisions. | 2 |
| Adjuvant radiation following clear margin resection of high t-stage cutaneous squamous cell carcinoma halves the risk of local and locoregional recurrence: a dual-center retrospective study. | 2 |
| Predicting adjuvant radiation therapy benefit in cutaneous squamous cell carcinoma with the 40-gene expression profile. | 2 |
| A prospective, multi-center clinical utility study demonstrates that the 40-gene expression profile (40-gep) test impacts clinical management for Medicare-eligible patients with high-risk cutaneous squamous cell carcinoma (cSCC). | 1 |
| Actionable risk thresholds for adjuvant radiation therapy and surveillance imaging in high-risk cutaneous squamous cell carcinoma. | 3 |
| Incorporation of the 40-gene expression profile (40-gep) test to improve treatment decisions in high-risk cutaneous squamous cell carcinoma (cSCC) patients: case series and algorithm. | 3 |
| Use of the 40-gene expression profile (40-gep) test in Medicare-eligible patients diagnosed with cutaneous squamous cell carcinoma (cSCC) to guide adjuvant radiation therapy (art) decisions leads to a significant reduction in healthcare costs. | 2 |
| Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma. | 2 |
| Integrating the 40-gene expression profile (40-gep) test improves metastatic risk-stratification within clinically relevant subgroups of high-risk cutaneous squamous cell carcinoma (cSCC) patients. | 2 |

**TABLE 2.**

| Consensus Statements and Recommendations | | |
|---|---|---|
| **Consensus Statement/Recommendation** | **Strength of Recommendation** | **Consensus Vote** |
| *The 40-GEP test provides statistically significant and clinically meaningful enhancement of the 3-year metastatic risk assessment of high-risk cSCC beyond traditional staging systems (AJCC8, BWH)* | A | 8/8 |
| *Data suggest that the 40-GEP test enhances local recurrence risk assessment of NCCN high-risk cSCC beyond traditional staging systems (AJCC8, BWH)* | B | 8/8 |
| *The 40-GEP test independently identifies cSCC patients that may benefit from adjuvant radiation therapy* | A | 8/8 |
| *In combination with clinicopathologic staging, the 40-GEP test identifies an additional subset of high-risk cSCC patients that may benefit from ART* | A | 8/8 |
| *In combination with clinicopathologic staging, the 40-GEP test identifies high-risk cSCC patients that may defer adjuvant radiation therapy* | B | 8/8 |
| *Utilization of the 40-GEP test can materially impact management decisions for clinicians treating patients with high-risk cSCC* | A | 8/8 |
| *The 40-GEP test can be used to guide clinical decision-making regarding surveillance imaging* | C | 8/8 |
| *The 40-GEP test is recommended for patients with high-risk cSCC tumors when clinically appropriate* | A | 8/8 |

LR (HR 2.6, *P*=0.005 and HR 6.5, *P*=0.013, respectively).[30] Further, the 40-GEP test can stratify patients by LR-free survival (LRFS) (log-rank, *P*=0.001), with a 3-year LRFS of 95.3% for Class 1, 85.5% for Class 2A, and 71.4% for Class 2B.[30] The 40-GEP test result also significantly stratifies LRFS in patients who had surgical intervention for cSCC (Mohs or wide local excision)and negative margins.[30] Given the limited literature on LR, the expert panel graded this statement a level B.

***Statement 3:*** *The 40-GEP test independently identifies cSCC patients that may benefit from adjuvant radiation therapy. (SORT Level A)*

Adjuvant radiation therapy (ART) following clear-margin surgery for high-risk cSCC can halve the risk of LR and locoregional recurrence.[31] Decision-making for which patients should be treated with ART can be clinically challenging. One study found significant variation in treatment decisions among patients with comparable clinicopathologic characteristics, indicating that reliance on these factors alone leads to inconsistent management choices.[32] In this study, 70% of patients who did not receive ART had clinicopathologic risk profiles similar to those who did, highlighting the variable application of ART despite similar clinical features.[32] Among the untreated patients, 4.3% were 40-GEP Class 2B, suggesting they may have benefitted from ART despite being classified as lower-risk by clinical features.[32] Additionally, another study found that patients with Class 2B who were treated with ART had an approximately 50% improvement in median 5-year disease progression rates and about 5-fold predicted time to a metastatic event vs those not treated with ART.[19] Independent validation has demonstrated that patients with Class 2B tumors treated with ART had significant improvements in metastasis-free survival compared with untreated patients (HR 0.17, *P*=0.01), which strengthens the evidence for using the 40-GEP to predict ART benefit in cSCC.[33]

***Statement 4:*** *In combination with clinicopathologic staging, the 40-GEP test identifies an additional subset of high-risk cSCC patients that may benefit from ART. (SORT Level A)*

Patients with a more moderate risk of metastasis may also benefit from ART. In 1 study, a benefit was observed for 40-GEP Class 2A ART-treated tumors, which had a median disease progression of 12% compared with 30.5% in ART-untreated tumors.[33] There was also an increase in median time to metastasis in ART-treated Class 2A tumors compared with ART-untreated (6.4 years-7.9 years, a 1.25-fold increase).[33] Additionally, ART-treated Class 2A tumors had a statistically greater time-to-metastasis distribution compared with ART-untreated (*P*<0.05)and also had a delay in disease progression.[33] When combined with clinicopathologic features, 40-GEP testing can aid decision-making for ART in this subgroup of patients.

The expert panelists noted that recommendations for ART in patients with cSCC must also consider other factors such as patient age, medical comorbidities, tumor location, treatment tolerance, patient preferences, and access to care.

***Statement 5:*** *In combination with clinicopathologic staging, the 40-GEP test identifies high-risk cSCC patients that may defer adjuvant radiation therapy. (SORT Level B)*

The 40-GEP test can identify patients with high-risk cSCC who may safely defer ART. While the 40-GEP test result should not be used in isolation, there is evidence for its utility when combined with clinicopathologic staging. In 1 study, one-third of patients with the highest-risk clinical features had 40-GEP Class 1 results, supporting the safety of ART deferral.[32] When applied to ART-eligible untreated patients, the 40-GEP result would have recommended ART deferral in 53%, consideration in 42%, and treatment in 5%.[32] Another study found that the significant benefit from ART was not observed for patients with 40-GEP Class 1 or Class 2A (*P*>0.05 for each), where disease progression was similar regardless of ART treatment, though this study was not powered to detect a benefit from Class 2A given the low-risk population of patients.[19] In fact, incorporation of 40-GEP test results into ART decision-making to defer ART for Class 1 results could save up to $784 million per year in direct costs.[34] A multidisciplinary panel identified key areas in clinical practice where 40-GEP testing offers distinct value, particularly in guiding de-escalation of care for patients in whom the potential risks of ART may exceed its benefits, and in informing decisions about elective nodal radiation.[35]

The panelists noted that there are limited data showing high-risk patients with certain clinicopathologic features, such as focal, incidental perineural invasion, can safely defer ART despite the 40-GEP result. A recent systematic review reported that local recurrence rates were 2.7% for BWH T1, 7.5% for T2a, 15.7% for T2b, and 33.5% for T3.[36] Therefore, the panelists highlighted that high-stage tumors such as T2b with a 40-GEP Class 1 result still have a high risk of metastasis, so ART would not necessarily be deferred.

***Statement 6:*** *Utilization of the 40-GEP test can materially impact management decisions for clinicians treating patients with high-risk cSCC. (SORT Level A)*

Evidence demonstrates that the 40-GEP test can meaningfully influence clinical management in high-risk cSCC.[17,18] In national survey-based studies, clinicians presented with high-risk cSCC vignettes altered management decisions in a risk-aligned manner based on 40-GEP results: Class 1 results led to reductions in recommendations for sentinel lymph node biopsy, ART or chemotherapy, follow-up frequency, and nodal imaging, whereas Class 2B results prompted appropriate escalation of

these interventions.[18,37,38] Similarly, lower-risk 40-GEP results consistently reduced recommendations for intensive therapies and follow-up, while higher-risk results increased clinical intervention intensity.[18,37,38]

Further, a multicenter prospective study of 59 Medicare-eligible patients reported that over 80% of clinicians found the 40-GEP test positively impacted management, 42% identified it as the single most influential factor, and 24% modified treatment plans based on results.[16]

Clinician perception of metastatic risk increased for 71.4% of patients with Class 2A tumors and decreased for 25.5% of those with Class 1 tumors, reflecting accurate interpretation.[16] While existing studies have relatively small cohorts, they provide high-quality, patient-centered evidence supporting the test's clinical utility.[18]

Despite the demonstrated value of the 40-GEP test, it continues to remain underutilized, with clinicians typically ordering it when results are likely to influence outcomes. Expert consensus supports 40-GEP use to guide escalation or de-escalation of care, highlighting its role as a clinically meaningful tool for individualized, risk-aligned management of high-risk cSCC.[35]

***Statement 7:*** *The 40-GEP test can be used to guide clinical decision-making regarding surveillance imaging. (SORT Level C)*

By accurately predicting metastatic potential, the 40-GEP test enables a shift toward tailoring the intensity of nodal assessment, such as selecting appropriate imaging modalities (ultrasound, MRI, or CT) or determining the need for nodal biopsy.[14] Its use should remain limited to NCCN-defined high-risk patients, where it informs surveillance imaging and follow-up strategies aligned with individual tumor risk.

Class 1 results support de-escalation of surveillance imaging and less frequent clinical follow-up for 40-GEP classified low-risk tumors if extensive disease is not present, while Class 2 results prompt discussion and consideration of more frequent imaging and closer monitoring for high-risk disease.[17] Importantly, these recommendations apply specifically to surveillance imaging, used for routine, risk-aligned monitoring, rather than diagnostic imaging, which is reserved for evaluation of symptomatic or suspected disease.

In a national survey of 244 clinicians experienced with 40-GEP testing, a Class 2B result was identified as one of the most influential high-risk factors guiding surveillance imaging decisions, comparable to extensive perineural invasion.[39] Notably, 95% of respondents cited a Class 2B result as the single most important factor prompting consideration of surveillance imaging, and clinicians overall viewed a 10% risk of local recurrence and a 20% risk of regional or distant metastasis as meaningful thresholds for initiating imaging.[39] While real-world data confirm that clinicians are incorporating 40-GEP results into surveillance imaging decisions, outcome-based evidence demonstrating improved survival or recurrence rates remains limited, highlighting a critical evidence gap.

***Statement 8:*** *The 40-GEP test is recommended for patients with high-risk cSCC tumors when clinically appropriate. (SORT Level A)*

The 40-GEP test is recommended for patients with high-risk cSCC when clinically appropriate, as it provides additional prognostic information beyond traditional clinicopathologic features. The panelists describe that the test is recommended when developing treatment or surveillance decisions and additional information is required for decision-making.

There are a number of limitations that are associated with use of traditional staging systems (AJCC8 and BWH). Current staging systems do not include all risk factors known to be associated with metastasis, and inconsistencies in their assessment have been documented.[13,14] For example, about 30% of metastatic cases are misclassified as low-risk T stages (eg, BWH T1/T2a), while about 75% of tumors categorized as high-risk (eg, BWH T2b/T3)do not metastasize.[8,9,29,40,41] These findings highlight that additional refinement of risk stratification in high-risk cSCC remains necessary. Further, biopsy specimens are frequently transected, which can hinder accurate assessment of tumor depth.[42,43] There is also interobserver variability in dermatopathology, with 1 study reporting discrepancies in 22% of cases, 40% of which involved nonmelanocytic neoplasms.[44-46] Collectively, these limitations contribute to the low sensitivity (23–46%)and positive predictive value (12–13%)observed in these staging systems.[8,9,29,47]

The panel described that clinically appropriate reasons for using the 40-GEP test include refining staging with metastatic and local recurrence risk stratification, guiding decision-making for ART, and guiding management decisions including imaging and clinical surveillance. Studies have demonstrated that the 40-GEP can reclassify a subset of tumors initially deemed high-risk by BWH or AJCC8 staging into lower-risk categories, thereby supporting safe deferral of ART or other interventions. On the other hand, it can also identify patients with aggressive tumors who may benefit from escalated management despite lower-risk clinical features. Thus, when used alongside established clinical and histopathologic criteria, the 40-GEP test enhances individualized risk assessment and supports evidence-based, precision care for high-risk cSCC.

## CONCLUSION

An expert consensus panel completed a comprehensive review of the literature and developed 8 consensus statements on the clinical utility and clinical impact of the 40-GEP test in enhancing management of high-risk cSCC. The 40-GEP test augments

staging accuracy by improving metastatic and local recurrence risk stratification beyond traditional staging systems (AJCC8, BWH), thereby better informing decisions regarding ART as well as guiding broader management strategies, including imaging and clinical surveillance. The expert panel believes that given the robust existing literature on the 40-GEP test, it should be utilized for patients with high-risk cSCC tumors when clinically appropriate.

## DISCLOSURES

Joshua Burshtein, Milaan Shah, Lauren DeBusk, Angela Rosenberg, Brooke Bartley, Danny Zakria, and Seemal Desai have no conflicts. Sarah Arron MD PhD is a consultant and speaker for Castle Biosciences, Regeneron. Investigator and consultant for Enspectra Health. Investigator for Premier/Sol-Gel. Consultant for Canfield, Lumenis. Speaker & Consultant, Castle Biosciences; Speaker and Consultant, Regeneron; Consultant, Replimune; Investigator, Premier/Sol-Gel; Consultant, Canfield; Consultant and Investigator, Enspectra Health; Consultant, Lumenis. David Cotter has served as an advisor, consultant, speaker, and/or study investigator for AbbVie, Alumis, Arcutis, BI, BMS, Castle, Celgene, Corevitas, Dermavant, DermTech, Galderma, Janssen, Journey, LEO, Lilly, Novartis, Organon, Pfizer, Prose, Regeneron, Sanofi, and UCB. Aaron Farberg has served as an investigator, consultant, and/or speaker for: Almirall, Castle Biosciences, Eli Lilly and Company, Johnson and Johnson, Pfizer, Regeneron, Sun Pharmaceutical Industries Ltd. Harrison Nguyen reports receiving consulting fees or research support from the following companies: AbbVie, Alumis, Amgen, Apogee, Arcuitis, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Galderma, Incyte, Johnson & Johnson, Leo Pharma, Novartis, Organon, Pfizer, Regeneron, Sanofi, Takeda, Sun Pharmaceuticals, UCB, Verrica Pharmaceuticals. Todd Schlesinger, MD has served as an investigator and/or consultant for AbbVie, Almirall, Apogee, Arcutis, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly, Flint Clinical, Genentech, Janssen, LEO Pharma, Oruka, Pfizer, Regeneron, Sun Pharma, Verrica, and UCB; served as an investigator for AbbVie, Allergan, Almirall, Arcutis, Aslan, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara Therapeutics, Castle Biosciences, Concert (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, HighlightII, Incyte, Janssen, Nimbus Therapeutics, Medicus, Novartis, Processa, Prolacta, Regeneron, Sanofi, SkinCure Oncology, Takeda, Trevi, and Verrica; is a shareholder in Bristol Myers Squibb, Chronicle Medical Software, Derma-Gene, Eli Lilly, Propedix and Remedly; has served as a consultant for Beiersdorf, Estee Lauder, Dermsquared, HTL Biotechnology, LaRoche Posay, L'Oreal, MJH Life Sciences, and RBC Consultants; and has received salary from Avant-Health. Nathalie Zeitouni: Castle Biosciences: Speaker Bureau and investigator. Sunpharma: investigator. Regeneron: Speaker Bureau, investigator, and consultant. Biofrontera: investigator and consultant. Stamford: investigator. Soligenix: investigator. Replimune: investigator. AlphaTau: investigator. Darrell Rigel has served as an investigator, consultant, and/or speaker for: Almirall, Beiersdorf, Inc., Castle Biosciences, Eli Lilly and Company, Ferndale Laboratories, Inc., Gore Range Capital, Johnson and Johnson Consumer Products Company, Kenvue, Pfizer, Primus Pharmaceuticals, SciBASE, SkinCure Oncology, Sun Pharmaceutical Industries Ltd., Takeda Pharmaceuticals, VYNE Therapeutics.

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## REFERENCES

1. Lukowiak TM, et al. Association of age, sex, race, and geographic region with variation of the ratio of basal cell to cutaneous squamous cell carcinomas in the United States. *JAMA Dermatol.* 2020;156(11):1192.
2. Genders RE, et al. Incomplete excision of cutaneous squamous cell carcinoma; systematic review of the literature. *Acta Derm Venereol.* 2020;100(6):adv00084.
3. Burshtein J, Schlesinger T. Managing advanced squamous cell carcinoma: a guide for the dermatology clinician. *J Clin Aesthet Dermatol.* 2025;18(8):20-26.
4. Sun L, et al. Association of disease recurrence with survival outcomes in patients with cutaneous squamous cell carcinoma of the head and neck treated with multimodality therapy. *JAMA Dermatol.* 2019;155(4):442-447.
5. Chua MST, et al. Parotid lymph-node metastases from cutaneous squamous-cell carcinomas: treatment outcome and prognostic factors following surgery and adjuvant radiotherapy. *Australas Radiol.* 2002;46(2):174-179.
6. Waldman A, Schmults C. Cutaneous squamous cell carcinoma. *Hematol Oncol Clin North Am.* 2019;33(1):1-12. doi:10.1016/j.hoc.2018.08.001
7. Amin MB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-99.
8. Karia PS, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol.* 2014;32(4):327-334.
9. Jambusaria-Pahlajani A, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol.* 2013;149(4):402.
10. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology for Squamous Cell Carcinoma (V1.2026).* Available at: www.nccn.org. Accessed February 27, 2025.
11. Stevenson ML, et al. Use of adjuvant radiotherapy in the treatment of high-risk cutaneous squamous cell carcinoma with perineural invasion. *JAMA Dermatol.* 2020;156(8):918.
12. Likhacheva A, et al. Definitive and postoperative radiation therapy for basal and squamous cell cancers of the skin: executive summary of an American Society for Radiation Oncology clinical practice guideline. *Pract Radiat Oncol.* 2020;10(1):8-20.
13. Wysong A, et al. Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2021;84(2):361-369.
14. Ibrahim SF, et al. Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test. *Future Oncol Lond Engl.* 2022;18(7):833-847.
15. Wysong A, et al. Integrating the 40-gene expression profile (40-GEP) test improves metastatic risk-stratification within clinically relevant subgroups of high-risk cutaneous squamous cell carcinoma (cSCC) patients. *Dermatol Ther.* 2024;14(3):593-612.
16. Saleeby E et al. A prospective, multi-center clinical utility study demonstrates that the 40-gene expression profile (40-GEP) test impacts clinical management for Medicare-eligible patients with high-risk cutaneous squamous cell carcinoma (cSCC). *SKIN J Cutan Med.* 2022;6(6):482-496.
17. Singh G, et al. Incorporation of the 40-gene expression profile (40-GEP) test to improve treatment decisions in high-risk cutaneous squamous cell carcinoma (cSCC) patients: case series and algorithm. *Clin Cosmet Investig Dermatol.* 2023;16:925-935.
18. Hooper PB, et al. Real-world evidence shows clinicians appropriately use the prognostic 40-gene expression profile (40-GEP) test for high-risk cutaneous squamous cell carcinoma (cSCC) patients. *Cancer Invest.* 2022;40(10):911-922.

19. Arron ST, et al. Association of a 40-gene expression profile with risk of metastatic disease progression of cutaneous squamous cell carcinoma and specification of benefit of adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys.* 2024;120(3):760-771.
20. Borman S, et al. Analytical validity of DecisionDx-SCC, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. *Diagn Pathol.* 2022;17(1):32.
21. Zakria D, et al. Incorporating a prognostic gene expression profile test into the management of cutaneous squamous cell carcinoma: an expert consensus panel report. *J Drugs Dermatol.* 2023;22(12):7691.
22. Ebell MH, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Med.* 2004;17(1):59-67.
23. Burshtein J, et al. The efficacy and safety of bimekizumab for plaque psoriasis: an expert consensus panel. *Dermatol Ther.* 2024;14(2):323-339.
24. Burshtein J, et al. Advances in technology for melanoma diagnosis and prognosis: an expert consensus panel. *J Drugs Dermatol.* 2024;23(9):774-781.
25. Burshtein J, et al. The association between obesity and efficacy of psoriasis therapies: an expert consensus panel. *J Am Acad Dermatol.* 2024:S0190-9622(24)03390-5.
26. Burshtein J, et al. Efficacy and safety of Hedgehog inhibitors for advanced basal cell carcinoma: an expert consensus panel. *J Drugs Dermatol.* 2025;24(5):465-471.
27. Burshtein J, et al. Risks of topical corticosteroid therapy and role for advanced targeted topical treatments for inflammatory skin diseases: an expert consensus panel. *Dermatol Online J.* 2025;31(1).
28. Masarwy R, et al. The prognostic value and clinical utility of the 40-gene expression profile (40-GEP) test in cutaneous squamous cell carcinoma: systematic review and meta-analysis. *Cancers.* 2023;15(9):2456.
29. Ruiz ES, et al. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital tumor classification system for cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2019;155(7):819.
30. Ratner D, et al. The 40-gene expression profile test identifies patients with National Comprehensive Cancer Network high-risk cutaneous squamous cell carcinoma at high risk of poor outcomes to inform management decisions. *SKIN J Cutan Med.* 2025;9(4):2426-2443.
31. Ruiz ES, et al. Adjuvant radiation following clear margin resection of high T-stage cutaneous squamous cell carcinoma halves the risk of local and locoregional recurrence: a dual-center retrospective study. *J Am Acad Dermatol.* 2022;87(1):87-94.
32. Moody BR, et al. Inconsistent associations between risk factor profiles and adjuvant radiation therapy (ART) treatment in patients with cutaneous squamous cell carcinoma and utility of the 40-gene expression profile to refine ART guidance. *Dermatol Ther.* 2024;14(4):861-873.
33. Ruiz ES, et al. Predicting adjuvant radiation therapy benefit in cutaneous squamous cell carcinoma with the 40-gene expression profile. *Future Oncol Lond Engl.* 2024;20(35):2737-2746.
34. Somani AK, et al. Use of the 40-gene expression profile (40-GEP) test in Medicare-eligible patients diagnosed with cutaneous squamous cell carcinoma (cSCC) to guide adjuvant radiation therapy (ART) decisions leads to a significant reduction in healthcare costs. *J Clin Aesthetic Dermatol.* 2024;17(1):41-44.
35. Gopal R, et al. Integrating 40-GEP testing to improve clinical recommendations for adjuvant radiation for cutaneous squamous cell carcinoma: multidisciplinary consensus guidelines. *J Clin Aesthetic Dermatol.* 2024;17(3 Suppl 2):S3-S8.
36. Zakhem GA, et al. Prevalence of poor outcomes in cutaneous squamous cell carcinoma by AJCC and BWH tumor stages: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2025;92(5):1064-1071.
37. Litchman GH, et al. Impact of a prognostic 40-gene expression profiling test on clinical management decisions for high-risk cutaneous squamous cell carcinoma. *Curr Med Res Opin.* 2020;36(8):1295-1300.
38. Rebeca T, et al. Impact of gene expression profile testing on the management of squamous cell carcinoma by dermatologists. *J Drugs Dermatol.* 2019;18(10):980-984.
39. Shah M, et al. Actionable risk thresholds for adjuvant radiation therapy and surveillance imaging in high-risk cutaneous squamous cell carcinoma. *SKIN J Cutan Med.* 2025;9(4):2444-2461.
40. Haisma MS, et al. Multivariate analysis of potential risk factors for lymph node metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. *J Am Acad Dermatol.* 2016;75(4):722-730.
41. Cañueto J, et al. Comparing the eighth and the seventh editions of the American Joint Committee on Cancer staging system and the Brigham and Women's Hospital alternative staging system for cutaneous squamous cell carcinoma: implications for clinical practice. *J Am Acad Dermatol.* 2019;80(1):106-113.e2.
42. Schmults CD, et al. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol.* 2013;149(5):541.
43. Thompson AK, et al. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol.* 2016;152(4):419.
44. Gaudi S, et al. Discrepancies in dermatopathology diagnoses: the role of second review policies and dermatopathology fellowship training. *J Am Acad Dermatol.* 2013;68(1):119-128.
45. Van Dijk MCRF, et al. Expert review remains important in the histopathological diagnosis of cutaneous melanocytic lesions. *Histopathology.* 2008;52(2):139-146.
46. Haggenmüller S, et al. Discordance, accuracy and reproducibility study of pathologists' diagnosis of melanoma and melanocytic tumors. *Nat Commun.* 2025;16(1):789.
47. Karia PS, et al. Comparison of tumor classifications for cutaneous squamous cell carcinoma of the head and neck in the 7th vs 8th edition of the AJCC Cancer Staging Manual. *JAMA Dermatol.* 2018;154(2):175.

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**Reference: 1.** Galderma Data on File [RD53.SPR.203914]. **2.** Galderma Data on File [RD.53.SPR.203908]. **3.** Garimella S, et al. J Drugs Dermatol. 2026;25(7):655–658. **4.** Goh C-L, et al. J Cosmet Dermatol. 2023;22:45–54. **5.** Whiting C, et al. J Drugs Dermatol. 2024;23(9):407636.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# A Moisturizer With *Centella asiatica* and Mandelic Acid Reduces Bruising and Speeds Recovery in Mature Skin

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## ABSTRACT

**Background:** Dermatoporosis is a chronic cutaneous insufficiency syndrome characterized by skin atrophy, purpura, bruising, delayed healing, and increased injury susceptibility. This study evaluated an investigational cream, GC (Galderma Laboratories, L.P., Fort Worth, TX), in subjects with mature, crepey, bruise-prone skin, using a novel method to assess bruise severity and duration.

**Methods:** This 12-week multicenter, randomized, blinded, in-use study recruited men and women aged 40 to 60 years with fragile, bruise-prone skin to apply GC cream twice daily to knees and thighs. A subset of 15 subjects underwent electric cupping on 1 randomized upper knee at baseline and week 12 to induce localized ecchymosis. Bruise severity was evaluated 15 minutes postinduction by investigators using standardized photography, and subjects captured daily images until resolution. Safety, tolerability, and subject satisfaction were assessed throughout.

**Results:** After 12 weeks of GC cream use, investigator-assessed bruise severity score was significantly lower than baseline (mean [SD] 3.27 [1.33] vs 4.13 [1.02]; [$P$=.0087]). Days to bruise resolution were also numerically shorter at week 12 compared with baseline (mean [SE] 6.33 [0.91] vs 8.00 [0.56]; [log-rank $P$=.3134]). Serial photography confirmed expected temporal evolution and resolution of bruising and supported improvement in investigator-assessed severity. Subject satisfaction was high, and there were no related adverse events.

**Conclusion:** Twelve weeks of twice-daily GC cream use significantly reduced bruise severity induced by electric cupping and helped bruises resolve faster. These findings support GC cream as an important new option to reduce bruise potential and improve skin health of subjects with dermatoporosis.

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## INTRODUCTION

Dermatoporosis is a cutaneous syndrome characterized by a progressive loss of skin strength and structural integrity.[1-4] Its clinical features include atrophy, purpura, lacerations, delayed healing, and, in advanced cases, dissecting hematomas.[1-4] Skin fragility may range from thinning, wrinkling, and laxity in midlife to marked atrophy with purpuric lesions in older individuals.[2,5,6] This spectrum reflects the varying contributions of intrinsic aging, photoaging, environmental exposure, and other factors that drive tissue decline.[5,6]

Visible bruising is a clinically relevant feature of dermatoporosis because it is readily apparent to subjects, can be distressing, and may indicate reduced tissue support.[7,8] In mature skin, dermal thinning, extracellular matrix deterioration, vascular fragility, and reduced subcutaneous support can lower the threshold for vessel rupture and ecchymosis.[7,8] Morphologic studies using reflectance confocal microscopy and ultrasonography have demonstrated structural changes in dermatoporosis, supporting the value of objective assessment of skin structure in this condition.[9]

The biology of bruise-prone mature skin is multifactorial. Intrinsic aging and chronic ultraviolet exposure alter epidermal function, collagen and elastin organization, dermal thickness, vascular support, and skin biomechanics.[10-13] Type I collagen loss contributes to dermal thinning and reduced tensile strength, while altered hyaluronan-CD44 signaling has been implicated in dermatoporosis-associated atrophy and purpura.[14-17] Cellular senescence provides another mechanistic framework for age-related skin fragility, as senescent fibroblasts and keratinocytes

have been described in aging skin, and emerging evidence suggests that senescence-related processes, including impaired clearance of photoaged fibroblasts, may contribute to dermal matrix disruption.[18-22] Together, these changes reduce perivascular and dermal support, making small vessels more susceptible to rupture after minor mechanical stress and increasing the likelihood of visible bruising.[7,8]

Current management of mature, fragile, bruise-prone skin remains limited and is largely supportive. Recommended approaches generally include photoprotection, gentle cleansing, moisturization, avoidance of unnecessary topical corticosteroid exposure, and mechanical protection of vulnerable skin, such as wearing protective clothing or limb coverings, selecting clothing that camouflages bruises when desired, and adopting lifestyle modifications to reduce avoidable minor trauma.[7,8,23-26] Published interventions for dermatoporosis or actinic purpura include topical retinaldehyde with defined-size hyaluronate fragments, topical vitamin C, collagen-oriented strategies, device-based approaches, and newer skin-fragility formulations.[27-30] Across these published interventions, study populations, anatomic sites, comparators, and endpoints differ, and bruise-specific outcomes are not consistently reported.[27-30]

Previously, Widgerow explored the effects of microdosed *Centella asiatica* and mandelic acid. In vitro data showed a synergistic decrease in expression of genes related to the senescence-associated secretory phenotype and associated inflammation; an ex vivo skin model validated reduced senescent cells with the microdosed formulation.[31] This novel formulation is now the investigational product, GC cream (Galderma Laboratories, L.P., Fort Worth, TX), that is being assessed in a multicenter, randomized, blinded, in-use clinical study of adults with mature, crepey skin. Given the potential for GC cream to modify cell senescence and improve dermal structure, we assessed its efficacy, subject satisfaction, and safety on induced bruise severity and duration.

## MATERIALS AND METHODS

This was a 12-week multicenter study conducted in the United States in accordance with Good Clinical Practice guidelines. Institutional Review Board (IRB) approval was obtained on July 30, 2025 (IRB ID: 14308; ClinicalTrials.gov number: NCT07398989). All subjects provided written informed consent.

### Subjects

Eligible subjects were males and females aged 40 to 60 years with a self-reported history of fragile and easily bruised skin, mild-to-moderate skin crepiness, photodamage, and firmness on the knees and lower thighs, defined as a score of 3 to 6 on the modified Griffiths scale (0 = none; 9 = most severe).[32] Subjects agreed to discontinue current topical body skincare products and replace them with the study product for the duration of the study. For this bruising component, subjects were required to be willing to undergo bruise induction on the upper knees. Key exclusion criteria relevant to bruising included allergy or hypersensitivity to anesthetics or lidocaine; diagnosed bleeding disorder; history of excessive bleeding after medical procedures; current use of blood-thinning medications, immunosuppressive medications, or systemic steroids; and history of keloid formation or hypertrophic scarring.

### Study Product

Subjects were instructed to apply the GC cream liberally twice daily, morning and evening, to the thighs and knees. Reapplication was encouraged throughout the day as needed. A supporting SPF moisturizer was provided, which subjects were instructed to use before sun exposure and to reapply as needed throughout the day. For at least 3 days before baseline, subjects used only their regular body cleansing product and avoided body moisturizers and other topical body skincare products. Subjects agreed to stop using current topical skincare products for the duration of the study.

### Bruise Induction

Bruise induction was performed and assessed at 1 selected center in this multicenter study. Bruising was induced on the randomized upper knee using an electric cupper (Smart Cupping Therapy Massager, manufactured by Revomadic) on heat level 0, suction level 5 or higher, and cupping mode 2 (continuous suction). Optional lidocaine could be applied before cupping. The cupper was applied for a minimum of 10 minutes, and the induced bruise was required to reach at least moderate visibility at baseline, defined as a score of 3 or higher on the 5-point Bruise Visibility Scale.[33] If needed, cupping could continue in 2-minute intervals until target bruise visibility was reached. A specific cupping procedure was established for each subject at baseline, which was repeated at week 12 in order to standardize bruise induction and assessment.

### Assessments

Clinical grading of bruise severity was performed at baseline and week 12 by the investigator based on a 5-point Bruise Visibility Scale. Standardized bruise photography was obtained 15 minutes after bruise induction using a handheld Canon EOS R100 camera with ranging lights (Canfield Scientific, Inc.). Images were captured under standard and cross-polarized filters. Subjects were also instructed to capture daily at-home images of the bruise, using similar positioning, timing, lighting, and location, when possible. Subjects submitted the images through a data-protected platform until the bruise was resolved or no longer visible. Bruising endpoints included change in bruise visibility/severity and change in bruise duration after 12 weeks of product use compared with baseline.

Subjects' perception, satisfaction, and preference regarding the study product were appraised via a self-assessment questionnaire at weeks 4, 8, and 12. Tolerability of the GC cream was evaluated at baseline and weeks 4, 8, and 12. Investigators assessed erythema, edema, and dryness of subjects' knees and lower thighs using a 4-point analog scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Adverse events (AEs) were monitored throughout the study, including potential study product–related events and procedure-related events relevant to cupping.

### Statistical Methods

Change from baseline in bruise visibility/severity and bruise duration was analyzed using a one-sample t-test; if normality assumptions were not met, the Wilcoxon signed-rank test was used. A decrease in bruise visibility/severity score indicated improvement, and a decrease in bruise duration indicated improvement in bruise resolution. Subjects with bruise resolution of more than 10 days were censored. For subject questionnaire data, a binomial sign test was applied to determine whether the proportion of combined favorable responses differed significantly from that of combined unfavorable responses. All statistical tests were performed at a two-sided significance level of 5%.

## RESULTS

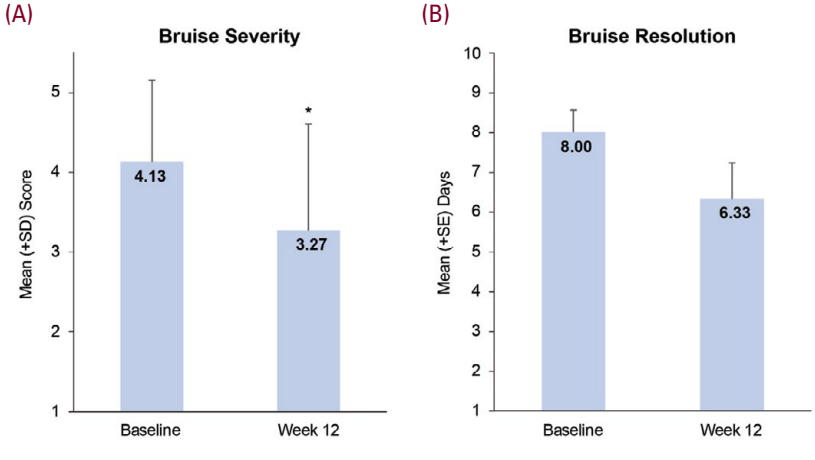
A total of 31 subjects were enrolled in the 12-week study across 2 centers; characteristics of the study population have been previously reported.[34] Baseline characteristics of the bruising cohort are summarized in Table 1. Sixteen (16) subjects were included at baseline, and 15 subjects had bruise assessments at week 12 and were evaluable for bruising-specific endpoints. Subjects in the bruising cohort were a mean of 54 years of age (range, 43–60 years), all identified as White/Caucasian, and 15 of 16 were female, non-Hispanic or Latin American, and had Fitzpatrick skin types II or III.

**TABLE 1.**

**Subject Disposition and Baseline Characteristics.** This cohort represents subjects who participated in the bruising assessments, including bruise induction, investigator-assessed bruise severity, standardized bruise photography, and daily at-home photographic follow-up until bruise resolution.

| Subjects | | N | % |
|---|---|---|---|
| Number | Enrolled | 16 | 100 |
| | Completed | 15 | 93.8 |
| Age | Mean | 54 | |
| | Minimum | 43 | |
| | Maximum | 60 | |
| Sex | Female | 15 | 93.8 |
| | Male | 1 | 6.3 |
| Race | White/Caucasian | 16 | 46.7 |
| Ethnicity | Hispanic/ Latin American | 1 | 26.7 |
| | Non-Hispanic/ Latin American | 15 | 93.8 |
| Fitzpatrick Skin Type | I | 0 | 0 |
| | II | 10 | 62.5 |
| | III | 5 | 31.3 |
| | IV | 1 | 6.3 |
| | V | 0 | 0 |
| | VI | 0 | 0 |

**FIGURE 1.** Bruise severity and resolution time at baseline and week 12. Bruise severity was assessed by the investigator on a 5-point scale (1 = barely visible, 3 = moderately visible, 5 = clearly visible).




Data shown are the mean (SD) of n=16 at baseline and n=15 at week 12; *$P$<.05 vs baseline. Time to bruise resolution was documented by daily subject photography. Data shown are the mean (SE) of n=16 subjects at baseline and n=15 subjects at week 12.

Mean (SD) investigator-assessed bruise severity decreased from 4.13 (1.02; n=16) at baseline to 3.27 (1.33; n=15) at week 12 (Figure 1A). The mean (SD) change from baseline was –0.87 (1.19; *P*=.0134). Bruise duration was assessed using daily subject-acquired photographs until bruise resolution or until the bruise was no longer visible. Documented bruise resolution in fewer than 10 days occurred in 12 of 16 subjects (75.0%) at baseline and in 13 of 15 (86.7%) at week 12. Mean (SE) time to resolution was 8.00 (0.56) days at baseline and 6.33 (0.91) days at week 12 (Figure 1B). Median time was 8.5 days and 7.0 days, respectively. The difference was not statistically significant (log-rank *P*=.3134). Resolution by day 7 was 31.3% at baseline versus 60.0% at week 12; by day 10, resolution was 75.0% versus 86.7%, respectively.

**FIGURE 2.** Representative clinical and subject photographs. (A) Subject 205 is a 54-year-old, non-Hispanic/Latin American, White/Caucasian female with Fitzpatrick skin type III. (B) Subject 213 is a 52-year-old, non-Hispanic/Latin American, White/Caucasian female with Fitzpatrick skin type II.

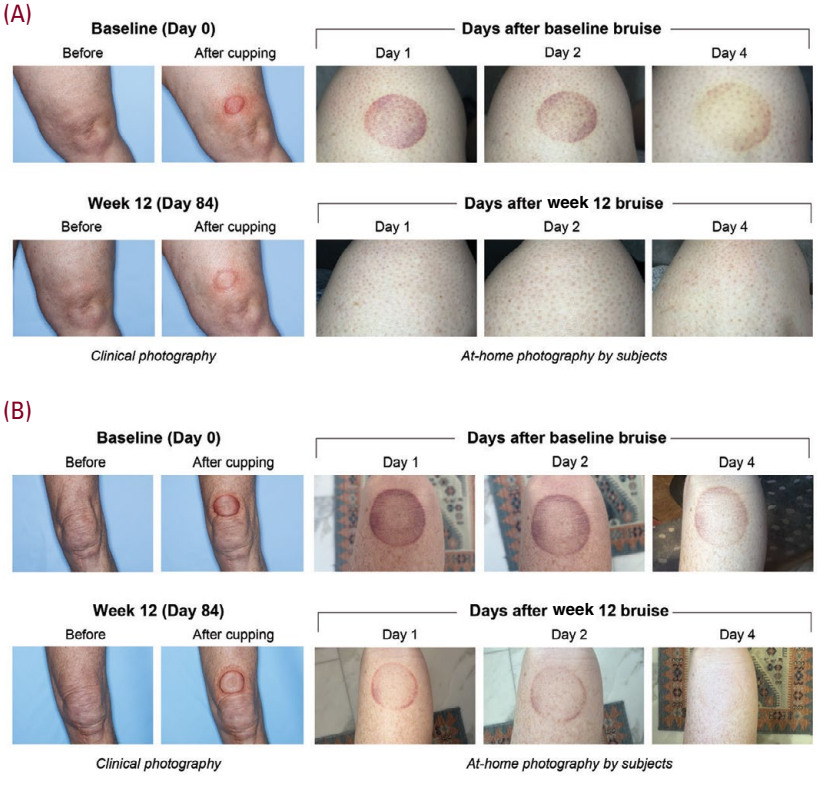



**FIGURE 3.** Cumulative probability of bruise resolution. Kaplan-Meier curves show the cumulative percentage of subjects with documented bruise resolution after bruise induction at baseline and week 12; censored subjects were included in the time-to-event analysis.

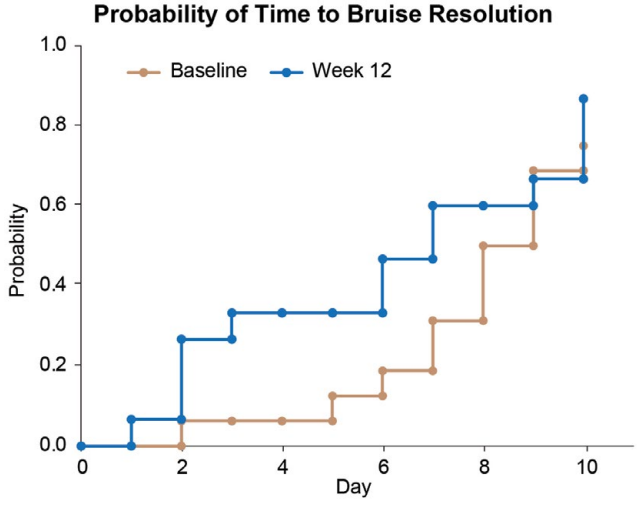


**FIGURE 4.** Subject self-assessments after 4 weeks and 8 weeks of GC cream use. Study subjects completed questionnaires after 4 weeks (N=30) and 8 weeks (N=31). Data shown are the mean favorable responses.

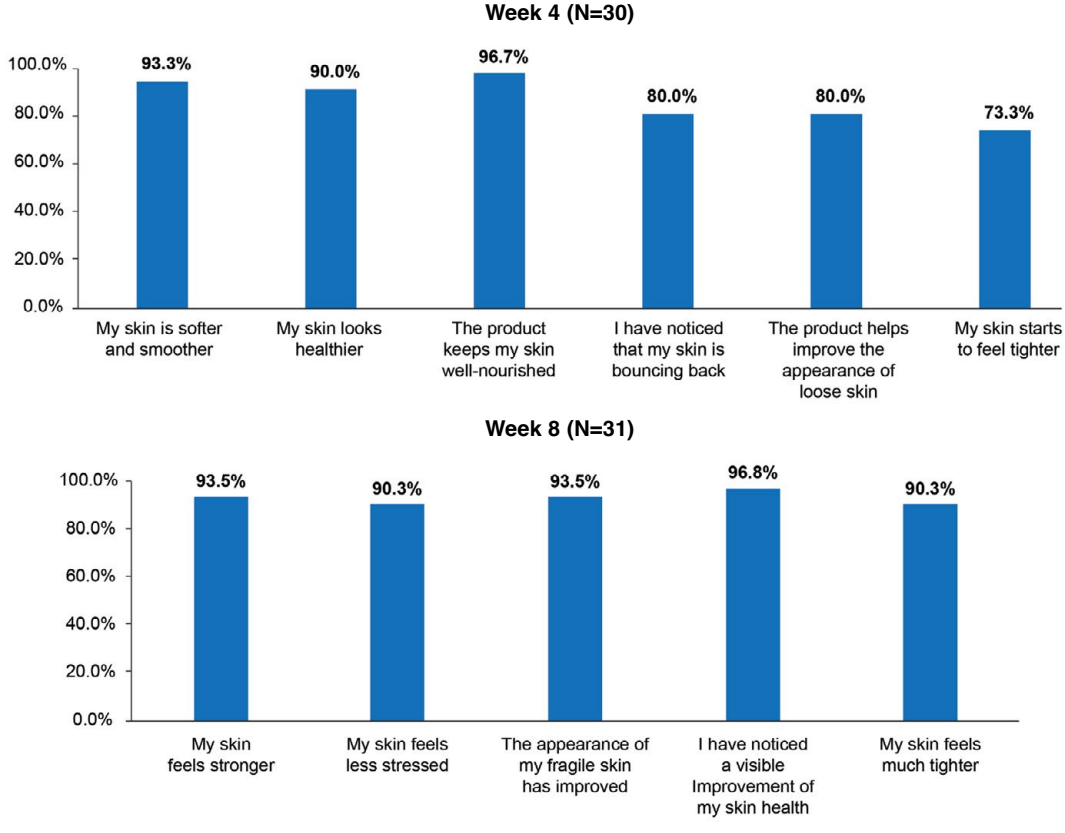



Figure 2 shows a representative series of daily at-home photographs from 2 subjects at baseline and week 12. The images show bruise evolution from early discoloration through fading and are consistent with mean severity and days to resolution shown in Figure 1.

Figure 3 shows the Kaplan-Meier plot of cumulative probability of bruise resolution over time. Half of the subjects documented resolution within 7 days or fewer after 12 weeks of GC cream use. At baseline, it took 8 days for bruising to resolve in half of subjects.

Clinical assessment of skin quality at baseline and week 12 for the full study population has been previously reported.[34] In the bruising subset, erythema and edema scores were 0.00 at baseline and at week 12. Mean (SD) dryness decreased from 0.56 (0.73) to 0.00 (0.00), with a mean change of –0.56 (0.73; *P*=.0074).

Subjects responded favorably to self-assessment questionnaires as early as 4 weeks of GC cream use and until the end of the study. Ninety percent (90.0%) of subjects reported that their skin looked healthier by week 4 and 93.5% reported that their skin felt stronger by week 8. After 12 weeks of use, consistent high satisfaction responses to questions about skin appearance ranged from 86.7% to 96.7%, while responses to questions about perceptions of skin health ranged from 90.0% to 93.3% (Figure 4). All subjects reported that they would continue using the GC cream (for responses to specific questions at week 12, see Ablon et al[34]).

No AEs related to the study product were observed or reported throughout the study. One subject was discontinued from the study because of a serious AE of equilibrium loss, which was not considered related to the study product.

## DISCUSSION

Bruising is a common concern among adults with dermatoporosis. In mature skin, dermal matrix deterioration, diminished connective tissue support, and impaired barrier function may lower the threshold for bruising after minor trauma.[7,8,25,35] In addition to being distressing, visible bruising can reflect reduced dermal support and vascular protection. Currently, there are few evidence-based topical options available to address bruise severity or resolution.[7,27]

This study shows that consistent twice-daily use of GC cream for 12 weeks helped lessen bruise severity and hasten bruise resolution in subjects with fragile, aging skin. Standardized clinical photography and daily subject-acquired photographs provided supportive visual documentation of bruise induction and longitudinal resolution, complementing the investigator-assessed severity and duration outcomes. Subjects were greatly satisfied with GC cream to improve overall skin appearance and restore skin health. There were no AEs related to the product, and subject satisfaction was high.

Traditionally, bruising studies have relied on invasive bruise induction methods, such as paintball pellets, dropped weights, and lasers, which can be difficult to standardize and reproduce.[36,37] Cupping with an electronic device was the bruise induction model chosen for this study due to the ability to carefully control the degree of suction and establish conditions for each subject that produced standardized bruising at baseline while maintaining the subject's safety. Cupping is an ancient procedure used in a variety of therapeutic settings. The application of controlled negative pressure disrupts tissues and capillaries, increases local blood flow, and creates an area of petechiae, purpura, or ecchymoses.[38] The resulting bruises are similar to those achieved from other invasive bruising methods. The use of subject-specific cupping conditions at baseline reduced intraindividual variation, and the use of the same subject-specific cupping conditions after 12 weeks of GC cream use helped reduce procedural variability. Daily subject-acquired photography supported longitudinal evaluation of bruise evolution. This is, to our knowledge, the first clinical study to use electric cupping to assess bruise severity and time to resolution. It offers an important new opportunity to expand evidence-based decision-making by dermatologists.

The rationale for evaluating a topical moisturizer in bruise-prone mature skin is biologically plausible. Moisturizers and barrier-supporting topical products may improve hydration and barrier integrity, while mature, fragile skin also reflects extracellular matrix deterioration and reduced tissue resilience.[25,39] Prior dermatoporosis research suggests that selected topical strategies may influence fragile skin biology, particularly through pathways related to hyaluronan signaling and dermal structure.[16,17,29] GC cream in particular was formulated based on ex vivo data showing that microdoses of *Centella asiatica* (0.005%) and mandelic acid (0.5%) reduced the number of senescent cells in the dermis and decreased inflammatory markers.[31] We have previously shown that this formulation improves skin hydration and increases expression of elastin and mechanical stretch with 12 weeks of use.[34,40] This is the first report of GC cream in a clinical study of bruising, and these results continue to support GC cream as a novel treatment for dermatoporosis.

A strength of this bruising-focused analysis is the integration of a standardized bruise induction method with both investigator assessment and longitudinal subject-acquired photography. The requirement that induced bruises reach at least moderate visibility supported interpretability of bruise visibility/severity and duration outcomes. The combination of in-clinic standardized imaging and daily at-home photography allowed evaluation of both immediate postinduction bruise appearance and subsequent bruise resolution.

Several limitations should be considered. First, the in-use study did not include a vehicle, untreated, or usual-care comparator arm; therefore, findings should be interpreted as within-subject changes after 12 weeks of GC cream use rather than controlled efficacy estimates. Next, the small number of subjects in the bruise cohort may limit generalizability to more diverse populations. Finally, bruises may differ by mechanism: everyday blunt-force trauma can involve pressure and shearing injury, whereas cupping produces tension-induced injury and rupture of small vessels. While the cupping model standardizes bruise induction and provides replicable control of the induction force, suction-induced bruises may not fully reproduce spontaneous bruising caused by everyday trauma. Despite these limitations, this study successfully deployed electric cupping as a standardized bruising method that could offer an alternative option for bruise models in future clinical settings.

## CONCLUSION

Using a novel model of controlled bruise induction, this study provides important data to support evidence-based decision-making for subjects with dermatoporosis at risk of bruising. Reduced bruise severity and decreased time to bruise resolution are clinically relevant improvements in skin health. In combination with prior findings where GC cream was shown to improve hydration, overall appearance, and elasticity of mature, crepey skin,[34,40] the current data further support this topical cream as an innovative agent that can address multiple aspects of dermatoporosis, including bruising.

## DISCLOSURES

Todd Schlesinger is an investigator and/or consultant for AbbVie, Almirall, Apogee, Arcutis Biotherapeutics, Benev, Biofrontera, Bristol Myers Squibb, Crown Aesthetics, Eli Lilly, Flint Clinical, Galderma, Genentech, Janssen, LEO Pharma, Oruka, Pfizer, Regeneron Pharmaceuticals, Sun Pharma, UCB, and Verrica; has served as an investigator for AbbVie, Allergan, Almirall, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Biofrontera, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Concert Pharmaceuticals (acquired by Sun Pharma), Cutanea Life Sciences, Dermavant Sciences, Eli Lilly, Galderma, HighlightII, Incyte, IPSEN, Janssen, Medicus,

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## REFERENCES

1. Dyer JM, Miller RA. Chronic skin fragility of aging: current concepts in the pathogenesis, recognition, and management of dermatoporosis. *J Clin Aesthet Dermatol.* 2018;11(1):13-18.
2. Kaya G, Kaya A, Sorg O, et al. Dermatoporosis: a further step to recognition. *J Eur Acad Dermatol Venereol.* 2018;32(2):189-191.
3. Kaya G, Saurat J-H. Dermatoporosis: a chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology.* 2007;215(4):284-294.
4. Wollina U, Lotti T, Vojvotic A, et al. Dermatoporosis - the chronic cutaneous fragility syndrome. *Open Access Maced J Med Sci.* 2019;7(18):3046-3049.
5. Ganceviciene R, Liakou AI, Theodoridis A, et al. Skin anti-aging strategies. *Dermatoendocrinol.* 2012;4(3):308-319.
6. Griffiths TW, Watson REB, Langton AK. Skin ageing and topical rejuvenation strategies. *Br J Dermatol.* 2023;189(Suppl 1):i17-i23.
7. Ceilley RI. Treatment of actinic purpura. *J Clin Aesthet Dermatol.* 2017;10(6):44-50.
8. Cho SI, Kim JW, Yeo G, et al. Senile purpura: clinical features and related factors. *Ann Dermatol.* 2019;31(4):472-475.
9. Menzinger S, Saurat J-H, Kaya G. Morphological analysis of dermatoporosis by in vivo reflectance confocal microscopy and ultrasonography. *Dermatopathology (Basel).* 2020;6(4):279-287.
10. Baumann L, Bernstein EF, Weiss AS, et al. Clinical relevance of elastin in the structure and function of skin. *Aesthet Surg J Open Forum.* 2021;3(3):ojab019.
11. Liang Y, Su W, Wang F. Skin ageing: a progressive, multi-factorial condition demanding an integrated, multilayer-targeted remedy. *Clin Cosmet Investig Dermatol.* 2023;16:1215-1229.
12. Rittie L, Fisher GJ. Natural and sun-induced aging of human skin. *Cold Spring Harb Perspect Med.* 2015;5(1):a015370.
13. Taylor CR, Stern RS, Leyden JJ, et al. Photoaging/photodamage and photoprotection. *J Am Acad Dermatol.* 1990;22(1):1-15.
14. Bar O, Valiukevičienė S. Skin aging and type I collagen: a systematic review of interventions with potential collagen-related effects. *Cosmetics.* 2025;12(4):129.
15. Bourguignon LY. Matrix hyaluronan-activated CD44 signaling promotes keratinocyte activities and improves abnormal epidermal functions. *Am J Pathol.* 2014;184(7):1912-1919.
16. Kaya G, Tran C, Sorg O, et al. Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med.* 2006;3(12):e493.
17. Nikolic DS, Ziori C, Kostaki M, et al. Hyalurosome gene regulation and dose-dependent restoration of skin atrophy by retinaldehyde and defined-size hyaluronate fragments in dermatoporosis. *Dermatology.* 2014;229(2):110-115.
18. Dimri GP, Lee X, Basile G, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci U S A.* 1995;92(20):9363-9367.
19. Dorf N, Maciejczyk M. Skin senescence—from basic research to clinical practice. *Front Med (Lausanne).* 2024;11:1484345.
20. Konstantinou E, Longange E, Kaya G. Mechanisms of senescence and anti-senescence strategies in the skin. *Biology (Basel).* 2024;13(9):647.
21. Xu X, Lu X, Chen X, et al. Elevated CD47 expression impairs elimination of photoaged fibroblasts by macrophages and serves as a potential biomarker for photoaging. *J Cosmet Dermatol.* 2025;24(4):e70098.
22. Zhang J, Yu H, Man MQ, et al. Aging in the dermis: fibroblast senescence and its significance. *Aging Cell.* 2024;23(2):e14054.
23. Cilluffo S, Bassola B, Beeckman D, et al. Risk of skin tears associated with nursing interventions: a systematic review. *J Tissue Viability.* 2023;32(1):120-129.
24. Gholizadeh S, Rice DB, Carboni-Jimenez A, et al. Effects of cosmetic and other camouflage interventions on appearance-related and psychological outcomes among adults with visible differences in appearance: a systematic review. *BMJ Open.* 2021;11(3):e046634.
25. Rajkumar J, Chandan N, Lio P, et al. The skin barrier and moisturization: function, disruption, and mechanisms of repair. *Skin Pharmacol Physiol.* 2023;36(4):174-185.
26. Syed HA, Masood S. Actinic purpura. In: *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing. 2026.
27. Guadanhim LRS, Miot HA, Soares JLM, et al. Efficacy and safety of topical or oral hydrolyzed collagen in women with dermatoporosis: a randomized, double-blind, factorial design study. *Dermatol Ther (Heidelb).* 2023;13(2):523-534.
28. Humbert P, Fanian F, Lihoreau T, et al. Bateman purpura (dermatoporosis): a localized scurvy treated by topical vitamin C - double-blind randomized placebo-controlled clinical trial. *J Eur Acad Dermatol Venereol.* 2018;32(2):323-328.
29. Kaya A, Saurat JH, Kaya G. Senotherapeutic effect of retinaldehyde and hyaluronate fragments in dermatoporosis. *Dermatopathology (Basel).* 2023;10(2):168-172.
30. Widgerow A, Grivet-Seyve M, Anjuwon S, et al. An innovative cream improves signs and symptoms of dermatoporosis in patients aged 65 and over. *J Drugs Dermatol.* 2025;24(4):352-356.
31. Widgerow AD, Ziegler M, Garruto JA, et al. Novel strategy for strengthening dermatoporotic skin by managing cellular senescence. *J Drugs Dermatol.* 2024;23(9):748-756.
32. Griffiths CE, Wang TS, Hamilton TA, et al. A photonumeric scale for the assessment of cutaneous photodamage. *Arch Dermatol.* 1992;128(3):347-351.
33. Scafide KN, Bahari G, Kutahyalioglu NS, et al. Development and pilot analysis of the Bruise Visibility Scale. *SAGE Open Nurs.* 2021;7:23779608211020931.
34. Ablon G, Emesiani C, Garimella S, et al. A novel moisturizer formulated with micronized *Centella asiatica* and mandelic acid improves mature, crepey skin. *J Drugs Dermatol.* 2026;9:833-838.
35. Bortolozo F, Rinaldi M, Souza P, et al. Dermatoporosis in upper limbs treated with polymethylmethacrylate microspheres using the BioSculpt® technique. *Cureus.* 2023;15(8):e43789.
36. Leu S, Havey J, White LE, et al. Accelerated resolution of laser-induced bruising with topical 20% arnica: a rater-blinded randomized controlled trial. *Br J Dermatol.* 2010;163(3):557-563.
37. Scafide KN, Sheridan DJ, Downing NR, et al. Detection of inflicted bruises by alternate light: results of a randomized controlled trial. *J Forensic Sci.* 2020;65(4):1191-1198.
38. Lowe DT. Cupping therapy: an analysis of the effects of suction on skin and the possible influence on human health. *Complement Ther Clin Pract.* 2017;29:162-168.
39. Lichterfeld-Kottner A, El Genedy M, Lahmann N, et al. Maintaining skin integrity in the aged: a systematic review. *Int J Nurs Stud.* 2020;103:103509.
40. Ablon G, Emesiani E, Garimella S, et al. Histological analysis shows a moisturizer formulated for dermatoporosis increases elastin content and improves skin elasticity. *J Drugs Dermatol.* 2026;25(10):962-966. doi:10.36849/JDD.10248

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

# Tranexamic Acid Mesotherapy for Melasma: An Interventional Study

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## ABSTRACT

**Background:** Tranexamic acid (TXA), an anti-fibrinolytic agent traditionally used to manage blood loss, has shown promising results in the treatment of melasma. Studies on the efficacy of intradermal TXA, with or without adjuvants, in treating melasma remain limited. There is also a lack of consensus on optimal dosing. This study aims to assess the efficacy of intradermal TXA for the treatment of melasma.

**Methods:** A total of 30 patients aged 20 to 60 years, diagnosed with melasma, were identified at the Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi, Pakistan, from October 2021 to April 2022. 0.05ml tranexamic acid (4mg/ml) was injected intradermally into the melasma lesions at 1cm intervals with a 0.5 mL insulin syringe and a 30-gauge needle. Intradermal TXA injections were repeated weekly for 12 weeks. Baseline and 4-, 8-, and 12-week modified Melasma Areas Severity Index (mMASI) were recorded. Clinical photographs were taken at 4, 8, and 12 weeks.

**Results:** Ages ranged from 20 to 60 years, with a mean age of 32.17 ± 6.70 years. 90.0% of patients were between 20 and 40 years of age (n=27). The mean baseline mMASI score was 8.58 ± 3.66. Mean mMASI scores at 4, 8, and 12 weeks were noted as 4.88 ± 2.22, 2.83 ± 1.37, and 1.38 ± 0.63, respectively. Over a 12-week treatment course of intradermal TXA, a significant reduction in mMASI score by 7.20± 3.71 was noted ($P$<0.0001).

**Conclusions:** Weekly TXA injections (0.05 mL, 4 mg/ml) for 12 weeks resulted in a significant reduction in mMASI score ($P$<0.0001).

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## INTRODUCTION

Melasma is a pigmentary disorder affecting over 5 million people in the United States.[1] The term "melasma" is derived from the Greek root word "melas," which means black, referring to the dark, hyperpigmented macules and patches that are clinically characteristic of this condition.[2] Sun-exposed areas, such as the face, are most commonly involved, particularly the bilateral cheeks, chin, and nose.[2] Melasma is more prevalent in women of childbearing age, especially among those with Fitzpatrick skin types IV-VI and of Hispanic, Asian, African, or Middle Eastern descent. Prevalence ranges from 8.8% among females of Latino descent living in the southern United States, 13.4 to 15.5% in a population of Arab Americans living in southeast Michigan, and up to 40% in some females of Southeast Asian populations.[3-5] In addition to the physical presentation, melasma can impact patients' quality of life, with many reporting frustration, embarrassment, and loss of confidence.[6]

The exact pathogenesis of melasma is complex and multifactorial, and evolving research suggests an interplay of keratinocytes, mast cells, gene regulation abnormalities, neovascularization, and basement membrane disruption.[7] Common triggers include sun exposure, pregnancy, oral contraceptives, hormone replacement therapy, cosmetics, medications, and racial or genetic effects.[8] Ultraviolet exposure results in an increase in melanogenic activity, leading to long-lasting epidermal pigmentation, specifically in darker skin.[9-11] Hormonal influences also play a role in some individuals, given the increased prevalence of melasma during pregnancy, oral contraceptive use, and hormone therapy. Melasma occurs in 14.5% to 56% of pregnant individuals, and 11% to 46% are associated with individuals on oral contraceptives.[12] During pregnancy, the increased production of pituitary hormones leads to the transcription of tyrosinase and dopachrome tautomerase, increasing pigmentation.[13] In addition, estrogen and progesterone have been associated with the disease due to increased expression of estrogen and progesterone receptors on melasma-affected skin.[14] Some cosmetic products have been noted to cause a phototoxic reaction, activating melasma.[15] Family history is another important risk factor, with more than 30% of patients reporting a family history of melasma.[8]

The treatment of melasma remains challenging, and efficacy varies widely between patients. Current treatments include photoprotection, avoidance of triggers, topical combination depigmenting agents, such as hydroquinone, tretinoin, and fluocinolone, laser therapy, intense pulsed light therapy, microneedling, and chemical peels.[5,10,16-19] Triple combination therapies were found to be more effective than monotherapy treatment of chemical peels, light, and laser therapy; however, 40% of patients developed erythema and peeling.[19]

Oral, topical, and intradermal tranexamic acid (TXA) has been used in the treatment of melasma as it inhibits neovascularization and melanogenesis.[20] Twelve weeks of oral TXA (250 mg BID for 3 months) showed a significant reduction in the modified Melasma Area Severity Index (mMASI) ($P$<0.05).[12] Oral TXA as an adjuvant to fluocinolone-based triple combination cream also showed a significant reduction in MASI scores at 4 weeks, with maintenance throughout 8 weeks.[21] However, oral TXA poses the risk of various systemic side effects, including thromboembolism, pulmonary embolism, and myocardial infarction.[22] Intradermal tranexamic acid is a relatively new, minimally invasive, and inexpensive treatment modality for melasma. In a prospective, randomized, open-label study of 30 patients receiving intradermal TXA microinjections monthly for 3 months, a 35.72% improvement in MASI score was noted.[23] In a nonrandomized split-face control trial comparing intradermal TXA and normal saline every 2 weeks for 12 weeks, intradermal TXA showed a reduced Hemi-modified MASI score and continued results at a 24-week follow-up.[24] When comparing intralesional TXA to topical hydroquinone, intralesional TXA showed significant improvement in MASI scores, a higher level of patient satisfaction, and fewer side effects.[20,25] An interventional study of 40 patients with melasma demonstrated equal efficacy of oral TXA with transepidermal TXA (with a dermaroller).[26] Batra et al report that although transepidermal TXA was more invasive and painful, this administration avoided the systemic side effects that often deter patients from oral TXA.[26]

Given the high prevalence of melasma in South Asian countries and the varying success of currently available treatments, we present an interventional study in Pakistan that evaluates the efficacy of intradermal TXA injections for patients with melasma in Pakistan.

## MATERIALS AND METHODS

From October 2021 to April 2022, adult patients aged 20 to 60 years, diagnosed with melasma, were identified at the Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi, Pakistan. The sampling technique was non-probability consecutive sampling. Exclusion criteria included pregnancy, lactation, oral contraceptive use, active infection, history of herpes simplex lesions on the face, and history of facial warts. 30 patients fulfilling the inclusion criteria were selected. Informed consent was obtained. Patient demographic data, including age, gender, disease duration, and past treatments for melasma, were recorded. All selected patients were clinically evaluated, and the baseline mMASI score was estimated. Modified Melasma Area Severity Index was calculated at baseline as well as at 4-, 8-, and 12-week follow-ups (Figure 1).

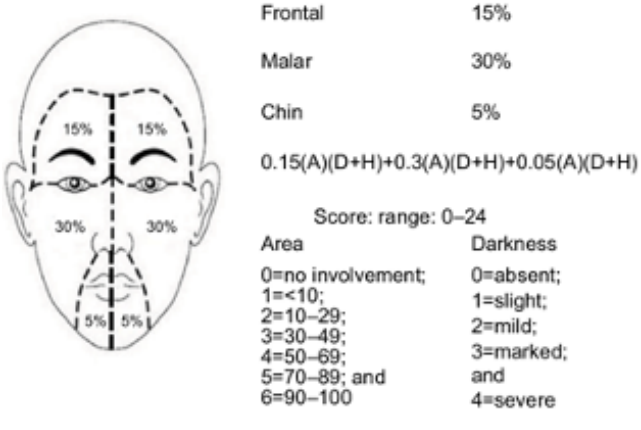
The area (A) of melasma involvement was graded from 0 to 5:

- 0 = No involvement
- 1 = less than 10% involvement
- 2 = 10% to 29% involvement
- 3 = 30% to 49% involvement
- 4 = 50% to 69% involvement
- 5 = 70% to 89% involvement

The darkness of pigmentation (D) and homogeneity (H) were graded from 0 to 4:

- 0 = absent
- 1 = slight
- 2 = mild
- 3 = marked
- 4 = maximum

**FIGURE 1.** Modified Melasma Area Severity Score (mMASI) grading.



After applying topical local anesthesia, 0.05 mL tranexamic acid (4 mg/ml) was injected intradermally into the melasma lesion at 1cm intervals with a 0.5 mL insulin syringe and a 30-gauge needle. This procedure was repeated weekly, and clinical photographs were taken at 4, 8, and 12 weeks. The collected data and mMASI scores at baseline, week 4, week 8, and week 12 were analyzed using SPSS 25.0. Means and standard deviations of age, melasma history duration, and mMASI score (pre- and post-treatment) were calculated. A paired sample t-test was performed to compare pre-and post-treatment mMASI scores, with a *P*-value of ≤ 0.05 indicating statistical significance.

## RESULTS

### Demographics

Demographics of study participants are displayed in Table 1. Eight (26.67%) of the study participants were male, and 22 (73.33%) were female. Ages ranged from 20 to 60 years, with a mean age of 32.17 ± 6.70 years. 90% of study participants (n=27) were aged between 20 and 40 years. The mean duration of melasma history was 6.28 ± 2.50 years. 47% of study participants had tried past treatments for melasma.

### mMASI Scores

The efficacy of intradermal TXA was measured in terms of the mean change in mMASI score. The mean change in mMASI score was calculated by the difference in mMASI score achieved at 4 weeks, 8 weeks, and 12 weeks of treatment from the baseline mMASI score. The mean mMASI score after treatment decreased from 8.58 ± 3.66 at baseline to 4.88 ± 2.22, 2.83 ± 1.37, and 1.38 ± 0.63 at 4, 8, and 12 weeks, respectively, as shown in Table 2. Clinical photographs were also taken pre-treatment and at 4, 8, and 12 weeks (Figure 2).

Stratification of mean change in mMASI after 4, 8, and 12 weeks with respect to gender, age, past treatments, and duration of melasma is shown in Table 3. Improvement of mMASI score was statistically significant when stratified for gender, age, past treatments, and duration of melasma (*P*<0.0001). There was, again, a statistically significant improvement in mMASI score (*P*<0.0001). The same stratification was performed with mMASI scores from 12 weeks, which also demonstrated a statistically significant reduction in all mMASI scores.

**TABLE 1.**

| Demographics of Study Participants (n=30) | | |
|---|---|---|
| **Demographics** | | **Number of Participants (n=30)** |
| Sex (male/female) | Male | 8 |
| | Female | 22 |
| Age (years) | 20-40 | 27 |
| | 41-60 | 3 |
| Duration of Melasma (years) | ≤5 | 8 |
| | >5 | 22 |
| Previous treatments attempted for melasma | Yes | 14 |
| | No | 16 |

**TABLE 2.**

| mMASI Score at Baseline and Weeks 4, 8, and 12 After Intradermal TXA Injections (n=30) | | | |
|---|---|---|---|
| | **Mean mMASI score** | **Standard Deviation** | ***P*-value** |
| Baseline | 8.58 | 3.66 | 0.0001 |
| 4 weeks | 4.88 | 2.22 | |
| 8 weeks | 2.83 | 1.37 | |
| 12 weeks | 1.38 | 0.63 | |

**FIGURE 2.** Clinical photographs of patients at baseline (A, E), 4 weeks of treatment (B, F), 8 weeks of treatment (C, G), and 12 weeks of treatment (D, H).



**TABLE 3.**

**Stratification of Mean Change After 4, 8, and 12 Weeks With Respect to Sex, Age, Duration of Melasma, and Previous Treatments for Melasma**

| Demographics | | Mean mMASI score (Baseline) | Mean mMASI score (4 weeks) | *P*-value (4 weeks) | Mean mMASI score (8 weeks) | *P*-value (8 weeks) | Mean mMASI score (12 weeks) | *P*-value (12 weeks) |
|---|---|---|---|---|---|---|---|---|
| Sex (male/female) | M | 9.58 ± 3.07 | 6.21 ± 2.89 | 0.0001 | 4.16 ± 1.85 | 0.0001 | 1.88 ± 0.95 | 0.0001 |
| | F | 8.22 ± 3.85 | 4.40 ± 1.82 | 0.0001 | 4.85 ± 0.73 | 0.0001 | 1.19 ± 0.35 | 0.0001 |
| Age (years) | 20-40 | 8.59 ± 3.73 | 4.93 ± 2.28 | 0.0001 | 2.89 ± 1.43 | 0.0001 | 1.41 ± 0.65 | 0.0001 |
| | 41-60 | 8.47 ± 3.64 | 4.50 ± 1.87 | 0.0001 | 2.35 ± 0.73 | 0.0001 | 1.10 ± 0.17 | 0.0001 |
| Duration of Melasma (years) | ≤5 | 8.08 ± 3.38 | 5.29 ± 2.52 | 0.0001 | 3.11 ± 1.66 | 0.0001 | 1.71 ± 0.73 | 0.0001 |
| | >5 | 9.02 ± 3.95 | 4.53 ± 1.94 | 0.0001 | 2.59 ± 1.06 | 0.0001 | 1.08 ± 0.33 | 0.0001 |
| Previous treatments attempted for melasma | Yes | 8.09 ± 3.97 | 4.27 ± 2.66 | 0.0001 | 2.90 ± 1.91 | 0.0001 | 1.36 ± 0.90 | 0.0001 |
| | No | 9.01 ± 3.44 | 5.42 ± 1.65 | 0.0001 | 2.77 ± 0.67 | 0.0001 | 1.39 ± 0.26 | 0.0001 |

## DISCUSSION

Weekly intradermal TXA injections (0.05 mL, 4 mg/mL at 1 cm intervals) over a period of 12 weeks significantly reduce the mMASI score. A statistically significant reduction in mMASI score is expected when gender, age, past treatments, and duration of melasma are stratified. The results of this study align with the limited literature available on the efficacy of intradermal TXA for melasma treatment. Khalili et al present a systemic review of 33 articles evaluating mesotherapy treatments for melasma.[27] The 2021 review found 28 articles about TXA, 4 articles about vitamin C, 2 articles about glutathione, and 2 articles about triamcinolone. Clinical trials of TXA mesotherapy showed similar efficacy to oral TXA; however, with a slower response rate. Clinical trials included in this review show that administration was often performed with an insulin syringe to allow for more control of placement and a 28 to 30 gauge needle for minimal pain. Interval distance was most commonly 1 cm (18 studies). TXA concentrations were most commonly 4 mg/cc (21 studies). Other concentrations included 10 mg/cc (1 study), 20 mg/cc (1 study), 50 mg/cc (1 study), and 100 mg/cc (3 studies). Sessions varied from weekly to biweekly to monthly to every 4 to 6 weeks.

TXA mesotherapy involves little downtime and minimal side effects, consisting primarily of transient bruising, pain, and erythema that is improved with ice pack application.[20,23-27] Khalili et al report that TXA mesotherapy presents as an efficacious adjunctive or alternative therapy for refractory melasma, patients with low compliance with topical treatments, and for those who may have contraindications to oral TXA.[27] The data on intradermal vitamin C, glutathione, and triamcinolone for melasma remain limited. The review emphasizes the importance of further studies to determine ideal concentrations and intervals for TXA mesotherapy. Our study contributes to the current literature by presenting that weekly intradermal TXA injections (0.05 mL, 4 mg/mL at 1 cm intervals) for 3 months in skin types III-VI showed significant reduction in mMASI score and clinical improvement.

## CONCLUSION

Weekly TXA injections (0.05 mL, 4 mg/ml) injections over a period of 12 weeks resulted in a significant reduction in mMASI score ($P<0.0001$). This study aims to contribute to the current literature to elucidate the efficacy as well as optimal route and dosing of intradermal TXA injections in the treatment of melasma.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

**IRB approval status:** Reviewed and approved by Pakistan RMU IRB (Reference No.: CPSP/REU/DER-2020-126-1252)

## REFERENCES

1. Grimes PE. Melasma. Etiologic and therapeutic considerations. *Arch Dermatol.* 1995;131:1453-1457. doi: 10.1001/archderm.131.12.1453.
2. Pandya AG and Guevara IL. Disorders of hyperpigmentation. *Dermatol Clin.* 2000;18:91-98, ix. doi: 10.1016/s0733-8635(05)70150-9.
3. Werlinger KD, Guevara IL, Gonzalez CM, et al. Prevalence of self-diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, *Tex Arch Dermatol.* 2007;143:424-425. doi: 10.1001/archderm.143.3.424.
4. El-Essawi D, Musial JL, Hammad A, et al. A survey of skin disease and skin-related issues in Arab Americans. *J Am Acad Dermatol.* 2007;56:933-938. doi: 10.1016/j.jaad.2007.01.031.
5. Pazyar N, Yaghoobi R, Zeynalie M, et al. Comparison of the efficacy of intradermal injected tranexamic acid vs hydroquinone cream in the treatment of melasma. *Clin Cosmet Investig Dermatol.* 2019;12:115-122. doi: 10.2147/CCID.S191964.
6. Zhu Y, Zeng X, Ying J, et al. Evaluating the quality of life among melasma patients using the MELASQoL scale: A systematic review and meta-analysis. *PLoS One.* 2022;17:e0262833. doi: 10.1371/journal.pone.0262833.
7. Kwon SH, Hwang YJ, Lee SK, et al. Heterogeneous Pathology of Melasma and Its Clinical Implications. *Int J Mol Sci.* 2016;17(6):824. doi: 10.3390/ijms17060824.
8. Handel AC, Miot LD and Miot HA. Melasma: a clinical and epidemiological review. *An Bras Dermatol.* 2014;89:771-782. doi: 10.1590/abd1806-4841.20143063.
9. Guinot C, Cheffai S, Latreille J, et al. Aggravating factors for melasma: a prospective study in 197 Tunisian patients. *J Eur Acad Dermatol Venereol.* 2010;24:1060-1069. doi: 10.1111/j.1468-3083.2010.03592.x.
10. Videira IF, Moura DF and Magina S. Mechanisms regulating melanogenesis. *An Bras Dermatol.* 2013;88:76-83. doi: 10.1590/s0365-05962013000100009.
11. Boukari F, Jourdan E, Fontas E, et al. Prevention of melasma relapses with sunscreen combining protection against UV and short wavelengths of visible light: a prospective randomized comparative trial. *J Am Acad Dermatol.* 2015;72:189-190 e181. 20141022. doi: 10.1016/j.jaad.2014.08.023.
12. KrupaShankar DS, Somani VK, Kohli M, et al. A cross-sectional, multicentric clinico-epidemiological study of melasma in India. *Dermatol Ther (Heidelb).* 2014;4:71-81. doi: 10.1007/s13555-014-0046-1.

13. Martin AG and Leal-Khouri S. Physiologic skin changes associated with pregnancy. *Int J Dermatol.* 1992;31:375-378. doi: 10.1111/j.1365-4362.1992.tb02662.x.
14. Tamega Ade A, Miot HA, Moco NP, et al. Gene and protein expression of oestrogen-beta and progesterone receptors in facial melasma and adjacent healthy skin in women. *Int J Cosmet Sci.* 2015;37:222-228. doi: 10.1111/ics.12186.
15. Doolan BJ and Gupta M. Melasma. *Aust J Gen Pract.* 2021;50:880-885. doi: 10.31128/ajgp-05-21-6002.
16. Srivastava RM, M. Rao, B. K. Noninvasive imaging tools in dermatology. *Cutis.* 2019;104:108-113.
17. Singh A and Yadav S. Microneedling: Advances and widening horizons. *Indian Dermatol Online J.* 2016;7:244-254. doi: 10.4103/2229-5178.185468.
18. Lee YJ, Shin HJ, Noh TK, et al. Treatment of melasma and post-inflammatory hyperpigmentation by a picosecond 755-nm alexandrite laser in Asian patients. *Ann Dermatol.* 2017;29:779-781. doi: 10.5021/ad.2017.29.6.779.
19. Rivas S and Pandya AG. Treatment of melasma with topical agents, peels and lasers: an evidence-based review. *Am J Clin Dermatol.* 2013;14:359-376. doi: 10.1007/s40257-013-0038-4.
20. Atefi N, Dalvand B, Ghassemi M, et al. Therapeutic effects of topical tranexamic acid in comparison with hydroquinone in treatment of women with melasma. *Dermatol Ther (Heidelb).* 2017;7:417-424. doi: 10.1007/s13555-017-0195-0.
21. Perveen S, Rubin A, Berger L, et al. A randomized trial of oral tranexamic acid with fluocinolone-based triple cream versus fluocinolone-based triple cream alone for the treatment of melasma. *J Drugs Dermatol.* 2022;21:321-322. doi: 10.36849/jdd.6099.
22. Cho HH, Choi M, Cho S, et al. Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd:YAG laser. *J Dermatolog Treat.* 2013;24:292-296. 20111227. doi: 10.3109/09546634.2011.643220.
23. Budamakuntla L, Loganathan E, Suresh DH, et al. A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. *J Cutan Aesthet Surg.* 2013;6:139-143. doi: 10.4103/0974-2077.118403.
24. Kaleem S, Ghafoor R and Khan S. Comparison of efficacy of tranexamic acid mesotherapy versus 0.9% normal saline for melasma: a split-face study in a Tertiary Care Hospital of Karachi. *Pak J Med Sci.* 2020;36:930-934. doi: 10.12669/pjms.36.5.2379.
25. Saki N, Darayesh M and Heiran A. Comparing the efficacy of topical hydroquinone 2% versus intradermal tranexamic acid microinjections in treating melasma: a split-face controlled trial. *J Dermatolog Treat.* 2018;29:405-410. doi: 10.1080/09546634.2017.1392476.
26. Batra J, Brar BK, Kumar S, et al. Tranexamic acid in melasma: comparative evaluation of therapeutic efficacy of oral tranexamic acid versus its transepidermal administration. *J Cutan Aesthet Surg.* 2022;15:394-399. doi: 10.4103/jcas.Jcas_237_20.
27. Khalili M, Amiri R, Iranmanesh B, et al. Safety and efficacy of mesotherapy in the treatment of melasma: a review article. *J Cosmet Dermatol.* 2022;21:118-129. doi: 10.1111/jocd.14644.

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# Central Centrifugal Cicatricial Alopecia and the Use of Xtressé Nutrient Supplement: A Case Series

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## ABSTRACT

Central Centrifugal Cicatricial Alopecia (CCCA) is a form of scarring alopecia characterized by patches of permanent hair loss that manifests on the crown of the scalp, progressively spreading outward in a centrifugal pattern.[1] This condition is predominantly observed in African American women. Treatment options for CCCA remain limited, with current treatments including topical and systemic corticosteroids and oral tetracyclines, with modest responses.[1] We present 2 cases of CCCA treated with Xtressé with notable improvement.

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## INTRODUCTION

Central Centrifugal Cicatricial Alopecia (CCCA) is characterized by progressive scarring and hair loss in the vertex or crown of the scalp and spreads centrifugally. CCCA is associated with inflammation and commonly affects women of African descent. Treatment goals include halting and preventing the progression of the disease and encouraging hair growth, but hair will not grow from permanently damaged hair follicles. No clear guidelines exist for the management of CCCA, and effective therapies remain limited. Xtressé is a commercially available nutrient supplement aimed to support hair growth. We present two cases of CCCA treated with Xtressé with notable improvement.

### Case Presentations

A 55-year-old African American female with a clinical and histopathologic diagnosis of CCCA presented with progressive hair loss (Figure 1). A biopsy performed at the right mid-crown revealed lymphocytic scarring alopecia, with a differential diagnosis including CCCA, lichen planopilaris, and contact dermatitis alopecia. Clinical correlation favored CCCA. She is currently treated topically with minoxidil, metformin, and clobetasol and advised to use bland, hypoallergenic, fragrance-free products; she received one treatment with intralesional triamcinolone. Two weeks after the biopsy, Xtressé nutrient supplements were added to the treatment regimen. Follow-up evaluations were conducted at 2 months (Figure 2) and 4 months (Figure 3) after initiating this plan.

**FIGURE 1.** Initial presentation.



**FIGURE 2.** Two month follow-up.



**FIGURE 3.** Four month follow-up.



A 42-year-old African American female with a past medical history of alopecia and anemia presented with a 10-year history of progressive hair loss, primarily affecting the frontal scalp and medial parietal region (Figure 4). At the time of presentation, she was using minoxidil and topical ketoconazole.

While she remained on oral minoxidil 2.5 mg, the new treatment regimen added a popular nutraceutical hair supplement, a nutraceutical shampoo, and metformin 10% compounded with triamcinolone. A follow-up scalp biopsy one month later revealed traction alopecia in the right frontal scalp and early/mild CCCA in the right midparietal scalp.

Two months later, doxycycline 40 mg (daily) and betamethasone (as needed) were added to her regimen. Over the next 6 months, she underwent 6 monthly intralesional triamcinolone injections and 3 sessions of hydrodermabrasion with growth factors (Figure 5). In the interim, she also presented with mild psoriasis vulgaris on the right temporal scalp and started on tapinarof cream. The psoriasis responded well. Despite the treatment plan, the CCCA continued to worsen. Xtressé hair supplements were added, and improvement was noted after 3 months (Figure 6).

**FIGURE 4.** Initial presentation.

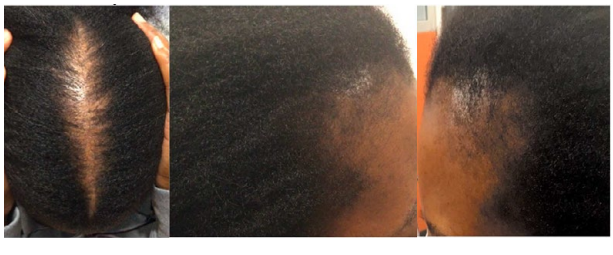


**FIGURE 5.** After six months of medical treatment.

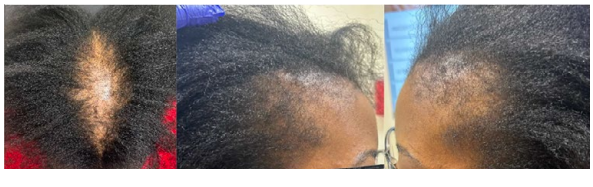
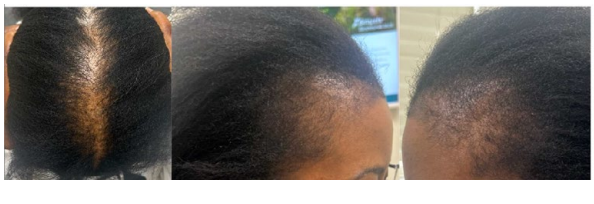


**FIGURE 6.** Results three months after Xtressé hair supplements were added to regimen.



## DISCUSSION

These cases illustrate the treatment response in 2 patients with CCCA after starting Xtressé supplements. While standard therapies such as topical minoxidil and intralesional corticosteroids are commonly used, the role of dietary supplements is not well-established. Xtressé contains several bioactive ingredients with potential roles in supporting hair follicle health. NAD+, a molecule involved in cellular metabolism and aging, has precursors have demonstrated the ability to promote hair growth in preclinical studies.[2] Pumpkin seed extract provides antioxidants that help reduce oxidative stress and inflammation.[3] Taurine, a beta-amino acid, supports mitochondrial function and provides antioxidant protection that can aid in the protection of follicular cells.[4] Saw palmetto reduces dihydrotestosterone (DHT) levels, a hormone associated with hair follicle miniaturization and thinning.[5] Improved hair growth was noted with the addition of Xtressé hair gummies. However, further studies are needed to determine the role Xtressé plays in the management of CCCA.

## CONCLUSION

These cases highlight Xtressé nutrient supplement's potential role as an adjunct to standard CCCA treatment. While positive effects were observed, further studies are needed to validate these findings. Nutritional supplementation may be able to help address CCCA-associated hair loss.

## DISCLOSURES

Dr Kindred serves in the following roles: Founding advisor for Xtressé, Advisory 17 board and speaker's bureau member for Eli Lilly, Sun Pharmaceuticals, and Janssen; board member for 18 Aerolase; speaker for UCB, Nutrafol, Novartis, and Regeneron; consultant for AbbVie and Pfizer; 19 member of the Janssen SOC Advisory Board and Steering Committee; editor for the Journal of the 20 National Medical Association (JNMA) and Cutis. Dr Gainers serves as a founding advisor for Xtressé. Bethel Desta has no conflicts of interest to disclose. All figures were created at https://BioRender.com.

## REFERENCES

1. Gabros S, Sathe NC, Masood S. Central centrifugal cicatricial alopecia. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559187/
2. Xu C, Dai J, Ai H, et al. β-Nicotinamide mononucleotide promotes cell proliferation and hair growth by reducing oxidative stress. *Molecules*. 2024;29(4):798. doi:10.3390/molecules29040798. PMID: 38398550
3. da Cruz GK, Martins MIM, Antunes FTT, et al. Evaluation of the efficacy and toxicity of oral and topical pumpkin oil on the hair growth of mice. *Acta Histochem*. 2022;124(4):151894. doi:10.1016/j.acthis.2022.151894. PMID: 35447441
4. Jong CJ, Sandal P, Schaffer SW. The role of taurine in mitochondria health: more than just an antioxidant. *Molecules*. 2021;26(16):4913. doi:10.3390/molecules26164913. PMID: 34443494
5. Sudeep HV, Rashmi S, Jestin TV, et al. Oral and topical administration of a standardized saw palmetto oil reduces hair fall and improves hair growth in androgenetic alopecia subjects - a 16-week randomized, placebo-controlled study. *Clin Cosmet Investig Dermatol*. 2023;16:3251-3266. doi:10.2147/CCID.S435795. PMID: 38021422

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# Q-switched Nd:YAG Laser for Extrafacial Lichen Planus Pigmentosus: A Case Series Highlighting Outcomes and Risks

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## ABSTRACT

Lichen planus pigmentosus (LPP) is a challenging pigmentary disorder that often affects extrafacial sites, yet most published data on laser treatment focus on facial involvement. We report 3 cases of biopsy-proven LPP treated with Q-switched neodymium: yttrium aluminum garnet (QS Nd:YAG) laser involving both facial and extrafacial areas. All patients experienced improvement in facial LPP, while outcomes on the neck, shoulders, and trunk were more variable. One patient developed koebnerized vitiligo after laser treatment to the neck, underscoring the need for caution in patients with underlying or suspected vitiligo. These cases highlight both the therapeutic potential and limitations of QS Nd:YAG lasers for extrafacial LPP and suggest that lower fluence approaches may offer safer alternatives in sensitive areas.

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## INTRODUCTION

Lichen planus pigmentosus (LPP) is an acquired dermal melanosis that typically affects photo-exposed and flexural surfaces. Q-switched neodymium: yttrium aluminum garnet (QS Nd:YAG) lasers target dermal melanosis and have shown promise in the treatment of LPP. The majority of reported cases using QS Nd:YAG are confined to the face,[1] despite at least 64% of cases of LPP presenting on extrafacial skin.[2] Here, we describe 3 cases of LPP with facial and extrafacial involvement treated with QS Nd:YAG laser, highlighting both therapeutic response and treatment-related complications.

## CASE SERIES

Three cases of biopsy-proven extrafacial LPP treated with QS Nd:YAG were included. In all cases, histopathology demonstrated lichenoid interface dermatitis with pigment incontinence, consistent with LPP.

**Case 1:** A 69-year-old male with Fitzpatrick type IV skin presented with LPP on the face, bilateral shoulders, chest, and lower back, refractory to topical corticosteroids. He underwent 16 treatments of QS Nd:YAG (spot size: 6 mm, fluence: 2.1–3.7 J, and frequency: 10 Hz; 1–2 passes for the face, 2–3 passes for the shoulders and chest, and 3–5 passes for the back) 1-4 weeks apart with moderate improvement of all sites (Figure 1). Additional maintenance treatments are currently being pursued.

**FIGURE 1.** (A-C) LPP of the lower back and bilateral shoulders before QS Nd:YAG. (D-F) Mild-moderate improvement of LPP after 16 treatments of QS Nd:YAG




**FIGURE 2.** (A-B) LPP of the neck and forehead before QS Nd:YAG. (C-D) Marked improvement of LPP after 10 treatments of QS Nd:YAG.




**Case 2:** A 44-year-old female with Fitzpatrick type IV skin presented with LPP on the face and neck. Her LPP was refractory to topical corticosteroids, hydroquinone cream, prednisone (tapered from 60 mg daily to 5 mg daily over 4 months) and low-dose isotretinoin (20 mg daily for 9 months). She underwent 10 treatments of QS Nd:YAG (spot size: 4–6 mm, fluence: 2.0–2.7 J, frequency: 10 Hz; 1–3 passes) 4 weeks apart. Within 3 treatments, improvement was noted. To enhance the results, the patient was started oral tranexamic acid 325 mg BID. Marked improvement was seen on the face and neck (Figure 2). Improvements were sustained after discontinuing tranexamic acid.

**Case 3:** A 42-year-old female with Fitzpatrick type IV skin presented with LPP on the face and neck. She was intermittently using topical corticosteroids, hydroquinone-based lightening creams, and retinoid creams without improvement. The patient underwent 6 treatments of QS Nd:YAG to the face (spot size: 6 mm, fluence: 2.5 J, frequency: 5 Hz; 1–2 passes) with significant improvement. Following improvement of the face, the patient elected to extent treatment to the neck. Because there was little improvement after 4 treatments (spot size: 6 mm, fluence: 2.5 J, frequency: 5 Hz; 1–2 passes), fluence was increased marginally for the fifth treatment (spot size: 6 mm, fluence: 2.8 J, frequency: 10 Hz; 1 pass). Two weeks later, she developed depigmented patches consistent with vitiligo (Figure 3). On Wood's lamp examination, a patch of vitiligo was noted on the lower back. Given no improvement after 7 weeks of observation followed by a 2-week course of high-potency corticosteroids, the patient was started on ruxolitinib 1.5% cream BID and achieved near complete repigmentation within 2 months.[3]

**FIGURE 3.** (A-B) LPP of the face and neck before QS Nd:YAG (C) Improvement in LPP of the face after QS Nd:YAG. (D) Laser-induced koebnerized vitiligo of the neck after a marginal increase in fluence. (E) Woods lamp highlighting depigmented patches. No improvement seen after 7 weeks of surveillance. (F) Complete resolution after a treatment course of ruxolitinib cream.




## DISCUSSION

In this report, we present 3 cases of LPP involving both facial and extrafacial areas with varied outcomes. All 3 patients experienced improvement in facial LPP with QS Nd:YAG, consistent with existing literature demonstrating favorable outcomes in facial LPP.[1] By contrast, treatments off the face required more sessions, with less consistent improvement. In case 3, laser treatment of the neck induced koebnerized vitiligo in a patient with previously unrecognized vitiligo vulgaris, emphasizing the need for caution. The variable results of QS Nd:YAG off the face may be due to several factors, including thinner epidermis and dermis of the neck and lower density of keratinocyte stem cells. The neck has fewer hair follicles, and since the hair follicle bulge is a major stem cell reservoir, this may limit regenerative capacity in extrafacial skin.[4] Both vitiligo and LPP are T-cell mediated disorders, suggesting a possible immunologic link. Although colocalization of LPP and vitiligo vulgaris has not been reported to our knowledge, cases of coexisting lichen planus and vitiligo have been described.[5] This case reinforces the importance of exercising caution when using energy-based treatments in patients with vitiligo vulgaris. All 3 patients in this series had Fitzpatrick type IV skin, a population particularly susceptible to both hyperpigmentation and hypopigmentation following laser procedures. This further highlights the importance of careful parameter selection and monitoring in skin of color.

QS Nd:YAG lasers can be effective in the treatment of LPP, particularly on the face; however, caution must be exercised when treating extrafacial areas. Results may be less predictable, dyspigmentation may be more permanent, and multiple treatments may be needed before improvement is noted. Low-fluence laser toning, as used in melasma, may offer a safer approach for treating extrafacial LPP due to its lower risk of triggering pigmentary alteration. Repeated treatments may increase the risk of pigmentary complications, including leukoderma.[6] Further studies are needed to establish optimal QS Nd:YAG protocols for treating LPP, particularly in extrafacial regions where safety and efficacy remain less predictable. Limitations include the small sample size, retrospective design, and absence of standardized outcome measures.

## DISCLOSURES

The authors have no conflicts of interest to disclose.

## REFERENCES

1. Shah DSD, Aurangabadkar DS, Nikam DB. An open-label non-randomized prospective pilot study of the efficacy of Q-switched Nd-YAG laser in management of facial lichen planus pigmentosus. *J Cosmet Laser Ther.* 2019;21(2):108-115. doi:10.1080/14764172.2018.1469770
2. Rutnin S, Udompanich S, Pratumchart N, et al Ashy dermatosis and lichen planus pigmentosus: the histopathological differences. *Biomed Res Int.* 2019;2019:5829185. doi:10.1155/2019/5829185
3. Bandali T, Voller L, Ko J, Kibbi N. Koebnerized vitiligo vulgaris following laser treatment of lichen planus pigmentosus successfully treated with topical ruxolitinib. *JAAD Case Reports.* Published online September 2024:S2352512624003072. doi:10.1016/j.jdcr.2024.07.033
4. Kiani MT, Higgins CA, Almquist BD. The hair follicle: an underutilized source of cells and materials for regenerative medicine. *ACS Biomater Sci Eng.* 2018;4(4):1193-1207. doi:10.1021/acsbiomaterials.7b00072
5. Veitch D, Kravvas G, Hughes S, Bunker C. A Rare Colocalization of Lichen Planus and Vitiligo. *Case Rep Dermatol Med.* 2015;2015:840193. doi:10.1155/2015/840193
6. Chen J, Yu N, Peng L, et al. Efficacy of low-fluence 1064 nm Q-switched Nd: YAG laser for the treatment of melasma: A meta-analysis and systematic review. *J Cosmet Dermatol.* 2022;21(7). doi:10.1111/jocd.15126

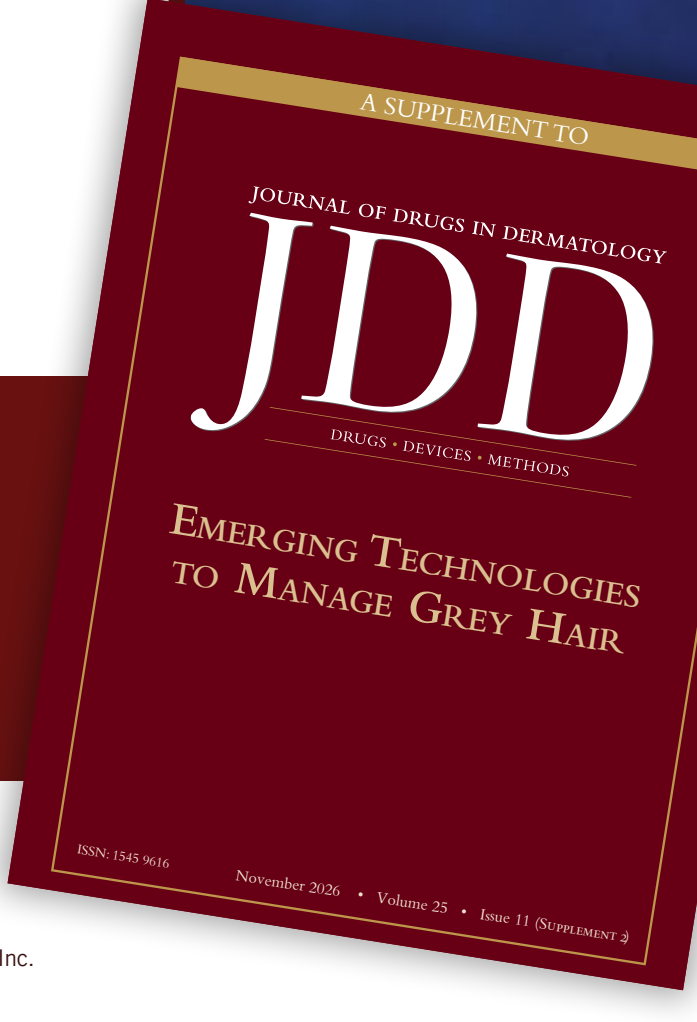
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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

# Celecoxib, Sirolimus, and Acitretin are Associated With Decreased Non-Melanoma Skin Cancer in the General Population

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## INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common malignancy in the United States, and a growing public health concern.[1] While a variety of prevention strategies exist for high-risk groups such as organ transplant recipients, few systemic agents have been evaluated for NMSC prevention in the general population.[1] Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has demonstrated antitumor effects through antiangiogenic and proapoptotic mechanisms, and studies in high-risk patients found that celecoxib significantly reduced the incidence of NMSC.[2] In addition, the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, inhibits keratinocyte proliferation, angiogenesis, and oncogenic signaling, with randomized controlled trials in organ transplant populations demonstrating sirolimus's association with significant reduction in NMSC incidence.[3] Similarly, retinoids have also been studied as chemopreventive agents, with trials demonstrating acitretin decreases risk for squamous cell carcinoma (SCC) in high-risk populations.[4] This large-scale retrospective cohort study evaluated the real-world impact of celecoxib, sirolimus, and acitretin use on the risk of NMSC development and related procedural interventions in the general population.

## MATERIALS AND METHODS

Within the TriNetX Research Network, we queried codes from the 10th revision of the International Classification of Diseases (ICD-10), Current Procedural Terminology (CPT), and RxNorm from August 1, 2015 to August 1, 2025. Three individual studies were conducted of adults (≥18) with ≥2 documented encounters for celecoxib (RxNorm: 140587), sirolimus (RxNorm: 35202), or acitretin (RxNorm: 16818) use were included and compared with a cohort without study medication exposure after propensity score matching (PSM). PSM was performed 1:1 on patient characteristics documented prior to study medication initiation, including demographics, comorbidities, and immunosuppressive medications/conditions (Table 1). Patients with inherited or acquired risk factors for NMSC, organ transplantation, previous or current systemic malignancy, exposure to multiple study medications or documentation of the target outcomes prior to study medication initiation were excluded. Primary outcomes included risk of NMSC development. Secondary outcomes included risk of Mohs micrographic surgery (MMS) (CPT: 17311-17315) and excision of malignant skin lesions (CPT: 1003243). Outcomes were evaluated using risk ratios (RR) and 95% confidence intervals (CI) at 5- and 10-year follow-up, with significance defined as $P$-value <0.05.

## RESULTS

After PSM, the celecoxib, sirolimus, and acitretin cohorts included 15,415, 2,288, and 5,915 patients per group, respectively (Table 2). Celecoxib use was associated with a significantly lower risk of developing NMSC at both 5 years (RR 0.83; $P$<0.001) and 10 years (RR 0.77; $P$<0.001), as well as reduced risk of MMS at 5 years (RR 0.81; $P$=0.0002) and 10 years (RR 0.77; $P$<0.001), and lower risk of excision for malignant skin lesions at 5 years (RR 0.73; $P$<0.001) and 10 years (RR 0.75; $P$<0.001). Similarly, sirolimus exposure was associated with a reduced risk of NMSC at 5 years (RR 0.49; $P$=0.018), with this protective effect persisting at 10 years (RR 0.49; $P$=0.01); however, ≤10 MMS and excision events were reported at both time points, and exact counts were suppressed by TriNetX privacy policies, precluding statistical analysis of these outcomes. Acitretin use was also associated with a significantly lower risk of NMSC at 5 years (RR 0.58; $P$<0.0001) and 10 years (RR 0.66; $P$<0.0001), along with markedly reduced risk of MMS at 5 years (RR 0.27; $P$<0.0001) and 10 years (RR 0.31; $P$<0.0001), and lower risk of excision for malignant skin lesions at 5 years (RR 0.35; $P$<0.0001) and 10 years (RR 0.41; $P$<0.0001).

**TABLE 1.**

**Baseline Demographic Characteristics of the Celecoxib, Sirolimus, and Acitretin Cohorts After Propensity Score Matching (PSM)**

| | Celecoxib Cohort [n (%)][1] (n=15415) | No Celecoxib Cohort [n (%)] (n=15415) | *P*-value | Sirolimus Cohort [n (%)] (n=2,288) | No Sirolimus Cohort [n (%)] (n=2,288) | *P*-value | Acitretin Cohort [n (%)] (n=5,915) | No Acitretin Cohort [n (%)] (n=5,915) | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| Age at Index, Mean ± SD[2] | 61.5 ± 13.5 | 61.6 ± 13.5 | 0.66 | 47.4 ± 18.6 | 47.5 ± 18.5 | 0.83 | 58.4 ± 16 | 58 ± 17 | 0.14 |
| Male | 5334 (34.60) | 5351 (34.71) | 0.84 | 1,033 (45.15) | 1,035 (45.24) | 0.95 | 3,045 (51.48) | 3,138 (53.05) | 0.09 |
| Female | 9037 (58.63) | 9027 (58.56) | 0.91 | 1,247 (54.50) | 1,246 (54.46) | 0.98 | 2,810 (47.51) | 2,767 (46.78) | 0.43 |
| White | 13396 (86.90) | 13395 (86.90) | 0.99 | 1,583 (69.19) | 1,586 (69.32) | 0.92 | 4,201 (71.02) | 4,209 (71.16) | 0.87 |
| Black or African American | 172 (1.12) | 173 (1.12) | 0.96 | 193 (8.44) | 195 (8.52) | 0.92 | 768 (12.98) | 790 (13.36) | 0.55 |
| Asian | 121 (0.79) | 120 (0.78) | 0.95 | 79 (3.45) | 62 (2.71) | 0.15 | 266 (4.50) | 243 (4.11) | 0.29 |
| Hispanic or Latino | 308 (2.00) | 307 (1.99) | 0.97 | 164 (7.17) | 176 (7.69) | 0.15 | 269 (4.55) | 275 (4.65) | 0.79 |
| Not Hispanic or Latino | 12482 (80.97) | 12514 (81.18) | 0.64 | 1,661 (72.60) | 1,624 (70.98) | 0.22 | 4,361 (73.73) | 4,412 (74.59) | 0.28 |
| Overweight and Obesity | 4793 (31.09) | 4798 (31.13) | 0.95 | 158 (6.91) | 158 (6.91) | 1.00 | 918 (15.52) | 851 (14.39) | 0.08 |
| Smoking | 1315 (8.53) | 1329 (8.62) | 0.78 | 70 (3.06) | 67 (2.93) | 0.79 | 667 (11.28) | 653 (11.04) | 0.68 |
| TNF-alpha Inhibitor Use[3] | 212 (1.38) | 190 (1.23) | 0.27 | 12 (0.52) | 10 (0.44) | 0.70 | 13 (0.22) | 11 (0.19) | 0.68 |
| JAK Inhibitor Use[4] | 29 (0.19) | 23 (0.25) | 0.41 | 10 (0.44) | 10 (0.44) | 1.00 | 10 (0.17) | 10 (0.17) | 1.00 |
| Systemic Corticosteroid Use | 381 (2.47) | 376 (2.44) | 0.85 | 32 (1.40) | 28 (1.22) | 0.60 | 48 (0.81) | 58 (0.98) | 0.33 |

[1]Percentages will not add up to 100% as certain patients did not have all demographics denoted comprehensively in their medical records.
[2]SD: Standard Deviation
[3]TNF-alpha: Tumor necrosis factor inhibitor
[4]JAK: Janus kinase

**TABLE 2.**

**Risk of Non-Melanoma Skin Cancer (NMSC), Mohs Micrographic Surgery (MMS), and Excision for Malignant Skin Lesion Following Celecoxib, Sirolimus, or Acitretin Use in the General Population**

| | Number of eligible individuals (number of outcomes, 5 years)[1,2] | Number of eligible individuals (number of outcomes, 5 years) | Risk Ratio (95% Confidence Interval) | *P*-value | Number of eligible individuals (number of outcomes, 10 years) | Number of eligible individuals (number of outcomes, 10 years) | Risk Ratio (95% Confidence Interval) | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | Celecoxib Cohort | No Celecoxib Cohort | | | Celecoxib Cohort | No Celecoxib Cohort | | |
| NMSC | 12070 (771) | 12848 (988) | 0.83 (0.76, 0.91) | <0.001 | 12070 (834) | 12848 (1120) | 0.77 (0.73, 0.86) | <0.001 |
| MMS | 14124 (521) | 14608 (668) | 0.81 (0.72, 0.90) | 0.0002 | 14124 (568) | 14608 (766) | 0.77 (0.69, 0.85) | <0.001 |
| Excision for malignant skin lesion | 14258 (381) | 14850 (541) | 0.73 (0.65, 0.84) | <0.001 | 14258 (421) | 14850 (587) | 0.75 (0.66, 0.85) | <0.001 |
| | Sirolimus Cohort | No Sirolimus Cohort | | | Sirolimus Cohort | No Sirolimus Cohort | | |
| NMSC | 2,247 (15) | 2,256 (31) | 0.49 (0.26-0.90) | 0.018 | 2,247 (18) | 2,256 (37) | 0.49 (0.28-0.86) | 0.01 |
| MMS | 2,276 (≤10) | 2,281 (15) | Not available | Not available | 2,276 (≤10) | 2,281 (15) | Not available | Not available |
| Excision for malignant skin lesion | 2,279 (≤10) | 2,284 (≤10) | Not available | Not available | 2,279 (≤10) | 2,284 (12) | Not available | Not available |
| | Acitretin Cohort | No Acitretin Cohort | | | Acitretin Cohort | No Acitretin Cohort | | |
| NMSC | 5,771 (116) | 5,208 (181) | 0.58 (0.46-0.73) | <0.0001 | 5,771 (156) | 5,208 (213) | 0.66 (0.54-0.81) | <0.0001 |
| MMS | 5,875 (36) | 5,598 (125) | 0.27 (0.19-0.40) | <0.0001 | 5,875 (50) | 5,598 (154) | 0.31 (0.23-0.42) | <0.0001 |
| Excision for malignant skin lesion | 5.885 (32) | 5,676 (88) | 0.35 (0.23-0.52) | <0.0001 | 5,885 (43) | 5,676 (102) | 0.41 (0.29-0.58) | <0.0001 |

[1]The number of eligible individuals from which the number of individuals with the target outcome is obtained (ie: "n") for each outcome differs slightly because each analysis was conducted independently. For each specific outcome (eg, NMSC, MMS, excision), only patients with that outcome documented prior to the sirolimus exposure were excluded.
[2]The number of eligible individuals differs from the overall matched cohort size because patients with documentation of the target outcome prior to the index date or with data outside the 20-year TriNetX lookback window were excluded from individual analyses.

## DISCUSSION

Our findings concur with prior studies and may reflect several mechanistic hypotheses. Celecoxib may reduce NMSC risk by suppressing UV-induced prostaglandin $E_2$ and immunomodulatory cytokines that promote keratinocyte proliferation, while directly inhibiting COX-2 activity in dysplastic epidermal cells, resulting in reduced epidermal hyperplasia, tumor burden, and markers of DNA damage.[2] Despite these potential chemopreventive effects, celecoxib use is limited by well-established risks, including cardiovascular events, gastrointestinal bleeding, renal toxicity, and hypersensitivity reactions, necessitating careful patient selection.[2] As for sirolimus, it appears to reduce skin cancer risk primarily by inhibiting mTORC1-dependent keratinocyte proliferation and disrupting NRF2-mediated antioxidant defenses, thereby enhancing oxidative stress-induced tumor cell death, an effect that is predominantly protective against SCC.[3] However, the drug's established immunosuppressive properties warrant careful patient selection.[3] Additionally, acitretin is thought to reduce NMSC risk by activating nuclear retinoic acid receptors to regulate gene transcription involved in keratinocyte differentiation, proliferation, and immune surveillance, though its use is limited by mucocutaneous toxicity, hyperlipidemia, hepatotoxicity, and strict teratogenic risk.[5] Our findings highlight the potential role of celecoxib, sirolimus, and acitretin as chemopreventive adjuncts to reduce NMSC risk in select patients who are not immunosuppressed. Limitations include reliance on ICD-10, CPT, and RxNorm coding, retrospective design, and lack of generalizability to patients with inherited or acquired skin cancer risk factors. Future studies incorporating prospective data and evaluation by NMSC subtype are needed.

## DISCLOSURES

SNT is an investigator/speaker for Bioventus, Kerecis, Boehringer Ingelheim, Regeneron, and CASTLE. Other authors have no conflicts of interest to declare.

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

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

## REFERENCES

1. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002–2006 and 2007–2011. *Am J Prev Med.* 2015;48(2):183-187. doi:10.1016/j.amepre.2014.08.036
2. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *JNCI.* 2010;102(24):1835-1844. doi:10.1093/jnci/djq442
3. Nicolás-Morala J, Mascaraque-Checa M, Gallego-Rentero M, et al. The m-TORC1 inhibitor Sirolimus increases the effectiveness of photodynamic therapy in the treatment of cutaneous squamous cell carcinoma, impairing nrf2 antioxidant signaling. *Int J Biol Sci.* 2024;20(11):4238-4257. doi:10.7150/ijbs.94883
4. George R, Weightman W, Russ GR, Bannister KM, Mathew TH. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol.* 2002;43(4):269-273. doi:10.1046/j.1440-0960.2002.00613.x
5. Russomanno K, Abdel Azim S, Patel VA. Immunomodulators for non-melanoma skin cancers: updated perspectives. *Clin Cosmet Investig Dermatol.* 2023;16:1025-1045. doi:10.2147/CCID.S362171

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

# Retrospective Review of Dermal Safety Studies of the Organic Sun Filter Bemotrizinol

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## INTRODUCTION

Bis-ethylhexyloxyphenol methoxyphenyl triazine (BEMT) is a UVA/UVB sun filter that has been approved for use in the European Union since 2000. In June 2026, the FDA approved BEMT as a new, safe, and effective UV filter for over-the-counter sunscreens in the US. BEMT was approved in the US at concentrations up to 6% in sunscreen products at maximum use and is used at concentrations of up to 10% in the Southern Common Market (Mercosur), China, and Europe, whereas in Japan BEMT is limited to 3%. We conducted a retrospective analysis of approximately 14,622 subjects who participated in clinical safety studies examining sunscreens formulated with BEMT for countries outside of the US.

## MATERIALS AND METHODS

The test subjects included adult volunteers from 18 to 70 years old. These subjects did not have a known history of allergies, skin diseases, or lesions. Exclusion criteria included: pregnancy, currently breastfeeding or planning to become pregnant during the study, having a history of skin cancer within the past 5 years, recent use of corticosteroids or other medications, compromised skin, or existing skin irritations on the test area. Tests were supervised by dermatologists and conducted at an independent laboratory. All clinical safety studies were approved by an Institutional Review Board, and all test subjects signed written informed consent forms.

A total of 108 formulas were assessed, which ranged from 0.1% to 6% BEMT concentration. BEMT formulations in the dataset are also combined with other UV filters, which are not described. Sunscreens in the tested dataset included commercialized and noncommercialized formulations. The categories were further divided into product types (Cream/Lotion, Pump/Spray, Serum, or Stick).

The Human Repeat Insult Patch Test (HRIPT) determines the potential of a product to cause irritation and/or allergic contact dermatitis. The Cumulative Irritation Test (CIT) test assesses the potential of a product to cause cumulative skin irritation. The Photo Toxicity Test (PT) study evaluates an induced photo irritation response to a product. The Photo Allergy Test (PA) study evaluates an induced photosensitization response. One hundred and eight studies were performed in 3 study centers in Latin America, Europe, and Asia. Specific protocols followed for each safety test can be found in Wilson et al 2025.

## RESULTS

A total of 14,622 subjects were evaluated in HRIPT, CIT, PT, or PA safety studies as summarized in Table 1. For HRIPT, 12,379 subjects evaluated 177 BEMT containing Cream/Lotion, Pump/Spray, Serum, or Stick formulations. These represent a range of commercial formulations that could contain BEMT. Of the 12,379 subjects in the HRIPT studies, there were no cases of

**TABLE 1.**

**Summary of BEMT Safety Studies Assessed**

| | HRIPT | | Photo Allergy | | Photo Toxicity | | Cumulative Irritation | |
|---|---|---|---|---|---|---|---|---|
| | # of Products | # of Subjects | # of Products | # of Subjects | # of Products | # of Subjects | # of Products | # of Subjects |
| Cream/ Lotion | 66 | 7324 | 17 | 456 | 31 | 532 | 19 | 560 |
| Spray | 42 | 4444 | 7 | 173 | 10 | 158 | 11 | 285 |
| Serum | 9 | 387 | 0 | 0 | 1 | 27 | 0 | 0 |
| Stick | 2 | 224 | 2 | 52 | 0 | 0 | 0 | 0 |
| Total | 117 | 12379 | 24 | 681 | 42 | 717 | 30 | 845 |
| Pass | -- | 12379 (100%) | -- | 681 (100%) | -- | 717 (100%) | -- | 845 (100%) |
| Fail | -- | 0 (0%) | -- | 0 (0%) | -- | 0 (0%) | -- | 0 (0%) |

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sensitization observed from any formulation containing BEMT. For assessments of potential photoallergy, phototoxicity, or cumulative irritation, a total of 2243 subjects tested Cream/Lotion, Pump/Spray, Serum, or Stick formulations containing BEMT.

The results of the retrospective assessment demonstrated that there were no cases of photoallergy, phototoxicity or cumulative irritation, observed from any formulation containing BEMT. These clinical safety study results demonstrate that formulations containing BEMT have a robust safety profile.

## DISCUSSION

Sun protection, including sunscreens, is essential for preventing skin cancer and the effects of photoaging such as mottled hyperpigmentation and wrinkles. We recently completed a retrospective assessment of the dermal safety of sunscreens containing existing organic UV filters (Wilson et al, 2025); this current retrospective assessment extends that work to include BEMT. Bis-ethylhexyloxyphenol methoxyphenyl triazine (BEMT), also known as bemotrizinol, is an oil-soluble organic compound used in sunscreens to absorb UV rays, protecting against both UVA and UVB rays. With a molecular weight of 627.80 g/mol and a solubility index, XLogP3 of 10.4, BEMT has unique physical/chemical properties that distinguish it from other sunscreen actives currently in use in the US market.[2] BEMT is a highly oil-soluble sun filter with a large relative molecular size which contributes to minimal, non-accumulative transdermal exposure and an ecological profile characterized by low environmental persistence, minimal bioaccumulation potential, and favorable ecotoxicity.[3,4] BEMT is an efficient broad-spectrum UV filter with multiple absorbance maxima reported: 310 nm in the UVB region and 343 nm in the UVA region of the solar radiation spectra[5], which results in broad-spectrum UV light protection.

The approval of BEMT by the FDA brings the first new organic UV filter to the US in over 20 years. BEMT is an efficient broad-spectrum UV filter, with protection from both UVA and UVB wavelengths. Furthermore, topical applications of BEMT containing sunscreen formulation containing 6% BEMT did not result in significant systemic exposure (D'Ruiz et al, 2023) likely a result of the large molecular weight of BEMT. The lack of systemic exposure further supports the safety profile of the new sun filter and also reinforces the importance of a robust assessment of dermal safety for BEMT.

The core hydroxyphenyl triazine structure of the BEMT chromophore exhibits extreme inherent photostability as well as an ability to photo-stabilize other more labile UV filters such as Avobenzone (Butyl Methoxydibenzoylmethane, BMDBM) when used in combination.[6] In addition, BEMT can combine with mineral sun filters such as Zinc Oxide and Titanium Dioxide, and will be generally regarded as safe and effective (GRASE) in the US, which can expand the range of sunscreen available.

The study shows no observed dermal irritation, sensitization, photoallergy, and photo irritation across a range of formulation types (ie, Cream/Lotion, Pump/Spray, Serum, or Stick), thereby reinforcing the overall safety profile of BEMT. One limitation of the current retrospective study supporting the safety of sunscreen formulations containing BEMT is extrapolating the results to other formulations. Although the study assessed safety in multiple forms of sunscreen formulations (creams, lotions, sprays, serums, and sticks), this extrapolation may not be applicable for every formulation form.

By analyzing data from over 14,000 subjects, this retrospective review provides strong evidence supporting the dermal safety of sunscreens containing BEMT. With these results, we aim to provide information to dermatologists and other medical professionals who may consult their patients on the safety and usage of BEMT products.

## DISCLOSURES

CMR, MDS, JDW, and SE are employees of Kenvue, which manufactures sunscreen products.

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## REFERENCES

1. PubChem. Bemotrizinol. Available at: https://pubchem.ncbi.nlm.nih.gov/20compound/bemotrizinol. Accessed 21 March 2026.
2. D'Ruiz CD, Plautz JR, Schuetz R, et al. Preliminary clinical pharmacokinetic evaluation of bemotrizinol - a new sunscreen active ingredient being considered for inclusion under FDA's over-the-counter (OTC) sunscreen monograph. *Regul Toxicol Pharmacol.* 2023;139:105344.
3. Tlili A, & Collard M. Environmental fate, hazard and risk assessment of the ultraviolet filter bemotrizinol in water and soil. In *SETAC Europe 35th Annual Meeting*. SETAC.
4. Shaath NA. (2007). *The encyclopedia of ultraviolet filters.* Carol Stream: Allured Publishing Corporation.
5. Sohn M, Baptiste L, Quass K, et al. (2021). Photokinetics of oil soluble 1, 3, 5-Triazine UV filters in combination with butyl methoxydibenzoylmethane or with diethylamino hydroxybenzoyl hexyl benzoate. *J Photochem Photobiol,* 8, 100073.
6. Wilson LT, Chu C, Wang SQ, et al. Retrospective review of dermal safety studies of organic sunscreens. *J Drugs Dermatol.* 2025;24(9):897-903.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

# The Current Landscape of Vitiligo Support Groups: An International Survey of Support Group Leaders

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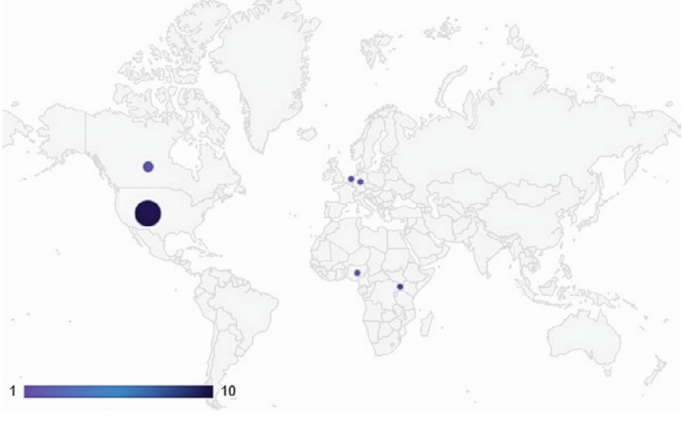
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## INTRODUCTION

Vitiligo can significantly impact the quality of life of affected individuals and their family members. Support groups provide numerous benefits, including allowing individuals to give and receive emotional and practical support.[1,2] This prospective, international, cross-sectional study aimed to characterize the current landscape and needs of support groups.

The authors designed an online survey with input from international support group leaders from the Global Vitiligo Foundation (GVF) and the Vitiligo International Patient Organizations Committee, which are largely recognized as major umbrella organizations for organized support groups globally. The English-language survey was distributed to 66 support group leaders from their respective networks. Sixteen group leaders responded from 6 countries: the United States, Canada, Uganda, Nigeria, Germany, and the Netherlands (Figure 1).

**FIGURE 1.** Map of survey respondents.




Among groups surveyed, founding years ranged from 1990 to 2024. Most groups met quarterly (37.5%) or monthly (25%) through virtual and in-person meetings (68.8%). Meeting places included community centers, restaurants, offices, business conference rooms, and cultural centers. Half the groups had official officers (50%), including the roles of president, secretary, treasurer, or executive board. The majority did not have dues or other membership requirements (68.8%). Nearly all the groups had a social media presence (93.8%), and 87.5% of group leaders reported social media as the most common route of member referral.

The most common age group was 35 to 54 years (mean 39%). Among US-based groups, the average racial/ethnic makeup was 51.9% Black, 34.2% White, 10% Mixed race, 8.3% Hispanic or Latino, 6.7% Other, and 5% Asian. Race/ethnicity data were restricted to US-based groups due to legal restrictions on demographic data collection in Europe. Women comprised over half of most groups, averaging 63.5%. Individuals with darker skin may experience increased disease visibility, contributing to greater psychosocial burden and reduced quality of life.[3,4] Additionally, women with vitiligo have been shown to experience greater impact on quality of life.[5]

The most popular topics covered were vitiligo treatments, living with vitiligo, mental health, and sun protection. Nearly half of groups hosted events targeted at individuals outside the vitiligo community (43.8%), and half had events for parents of affected children (50%). The most common group goals included providing emotional support, spreading awareness, and sharing practical information.

While less than half of the groups were affiliated with an academic center or hospital (43.8%), most had medical professionals attend meetings (62.5%), of whom 70% were dermatologists, and of that group, 70% served in an official role.

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**TABLE 1.**

| Umbrella Organizations for Vitiligo Support Groups | |
|---|---|
| **Parent Organizations** | ***n*** |
| Vitiligo International Patient Organizations Committee | 3 |
| VitFriends | 3 |
| Global Vitiligo Foundation | 2 |
| Global Skin Foundation | 1 |
| German Vitiligo Association | 1 |
| Vstrong | 1 |
| Litty Ligo | 1 |

The overwhelming majority of support group leaders reported members developed a deeper understanding of their condition through participation (93.8%). While most reported feeling confident facilitating events, and three-quarters held other leadership positions, nearly all (93.8%) were interested in additional training to help run their support group. Many groups were chapters of larger vitiligo organizations (Table 1), and most were part of the Global Vitiligo Foundation Community (68.8%). The majority (75%) had members who attended the US World Vitiligo Day conference.

While over half of groups had funding (56.3%) from donations, member contributions, grants, health insurance, and government support, half still cited funding as their largest challenge. Half reported burnout and difficulty recruiting volunteers as their second greatest challenge. Other challenges faced include organizing meetings, lacking a medical advisor, and a lack of public awareness and supportive policies.

Overall, there was significant global heterogeneity in group membership and size, leadership structure, and meeting frequency. Commonalities included shared primary goals and the key role of social media in group functioning. Many groups had a predominance of Black and female members. This study was limited by survey nonresponse bias, reliance on group leader-reported data, and the potential omission of additional vitiligo support groups not identified. Factors contributing to the response rate include that the survey was only distributed in English, which may have limited participation from non-English-speaking regions, and some support groups may have been inactive at the time of survey distribution. Finally, as many support group leaders serve in a voluntary capacity, survey completion may have been limited by competing priorities. Findings from this study highlight several important findings, including the current benefits and needs of support groups, the need for increased funding to expand programming and leadership training for group facilitators, and lastly that dermatologists may assist vitiligo support groups by serving as medical advisors.

## DISCLOSURES

Dr. Elbuluk has served as a consultant, advisory board member, and/or speaker for Arcutis, Incyte, La Roche Posay, Beiersdorf, Eli Lilly, Pfizer, Takeda, Abbvie, Janssen, Sanofi, L'Oreal, McGraw Hill, Dior, Medscape, Kao USA, Skinceuticals, Veradermics, Canfield, Kenvue, Teva. She has grant funding from Pfizer and Eli Lilly, has received royalties from McGraw-Hill and has stock options in VisualDx. Dr Grimes has served as an investigator, consultant, advisory board member, and/or speaker for Galderma, Clinuvel, L'Oreal, Johnson & Johnson, LaserOptek, Versicolor Technologies, MERCK, Dermbiont, VYNE Therapeutics, RAPTTherapeutics, Incyte, Pfizer, AbbVie/Allergan, SkinBetterScience, Klotho Skincare, Mother Science, Medscape, and Beiersdorf. She is the founder and director of the Vitiligo and Pigmentation Institute. She has stock options in Versicolor Technologies. Dr Huggins has served as an investigator, consultant, and/or advisory board member for Arcutis, Avita, Clinuvel, Incyte, Novartis, Mitsubishi, Pfizer, and The Immune Tolerance Network. He is a board member of the Global Vitiligo Foundation (GVF) and chair of the GVF Community Committee. The remaining authors have no disclosures to report.

**Ethics Statement:** This study was reviewed and deemed exempt by the University of Southern California Institutional Review Board. Study ID UP-24-00832

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

## REFERENCES

1. Geisler A, O'Connell KA, Pandya R, et al. Importance of and instruction for starting a vitiligo patient support group. *Dermatol Online J.* 2022;28(6). doi:10.5070/d328659723
2. Smith ZI, Wang JF, Elbuluk N, et al. A multi-centered case-control study of vitiligo support groups and quality of life. *J Drugs Dermatol.* 2021;20(6):672-675. doi:10.36849/jdd.2021.5706
3. Bibeau K, Ezzedine K, Harris JE, et al. Mental health and psychosocial quality-of-life burden among patients with vitiligo: findings from the Global VALIANT Study. *JAMA Dermatol.* 2023;159(10):1124-1128. doi:10.1001/jamadermatol.2023.2787
4. Mehta N, Gupta V. Psychosocial impact of vitiligo in patients with skin of color. *Dermatol Rev.* 2022;3(5):269-275. doi:https://doi.org/10.1002/der2.148
5. Samela T, Malorni W, Matarrese P, et al. Gender differences in vitiligo: psychological symptoms and quality of life assessment description. *Front Psychol.* 2023;14:1234734. doi:10.3389/fpsyg.2023.1234734

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

# Biomarkers and Clinical Disease Severity in Hidradenitis Suppurativa: A Linear Mixed-Effects Modeling Study

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*To the Editor,*

Hidradenitis suppurativa (HS) is a systemic inflammatory disorder with a multifactorial pathophysiology that remains incompletely understood. Previous research has demonstrated that specific inflammatory markers, including leukocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) are significantly associated with severe disease as defined by HS-Physician Global Assessment (HS-PGA) score.[1] Importantly, however, no studies have validated the sensitivity of these markers with fluctuations in disease activity over time. Herein, we investigate the utility of various biomarkers in continuous outcome monitoring for patients with HS and assess their sensitivity in a real-world setting.

A retrospective chart review was conducted to identify patients seen at Montefiore Medical Center between September 1, 2017, and May 1, 2025. Patients were included if they had clinical and laboratory markers of disease severity at baseline and at ≥4 follow-up visits. Collected data included patient demographics, comorbid medical conditions, HS-PGA score, numerical rating scale for pain (NRS-pain) score, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), leukocyte count, ESR, CRP, and IL-6 across repeat patient visits.

Linear mixed-effects models with patient identifier (MRN) as a random intercept were employed to examine associations between disease severity and laboratory markers over time. Disease severity was modeled continuously using the HS-PGA score. Analyses were conducted using R (version 4.2.1).

The cohort was predominantly female (66%) and Black (49%). The average age at intake was 35.5 years (SD 13.52); consistent with the epidemiological profile of HS in the US population at large.[2] Patients had a median of eight visits (IQR 6) where primary outcome measures were recorded, with a median interval between visits and a median follow-up duration of 70 days (IQR 84) and 878 days (IQR 695), respectively. A detailed summary of visit characteristics, demographic information, and comorbid medical conditions can be found in Table 1.

Longitudinal analysis of laboratory markers revealed positive associations between HS-PGA and leukocyte count (β=0.03, $P<0.001$), CRP (β = 0.14, $P<0.001$), ESR (β = 0.012, $P<0.001$), and IL-6 (β =0.005, $P<0.001$) indicating that higher inflammatory marker levels correlated with greater disease severity. Conversely, significant negative associations were observed between HS-PGA and hemoglobin (β=-0.16, $P<0.001$), hematocrit (β=-0.05, P<0.001), and mean corpuscular volume (β=-0.02, $P<0.001$). A detailed summary of associations between clinical disease severity and the various inflammatory markers studied can be found in Table 2.

Extending beyond previous work, we demonstrate statistically significant longitudinal associations between clinical disease severity and serum biomarkers known to be associated with HS.[1,3] Establishing the sensitivity of specific biomarkers to changes in disease state over time supports their use as validated primary endpoints for HS clinical trials and prospective studies, which largely rely on subjective outcome measures to evaluate drug efficacy at present.[4,5] Moreover, the effect size estimates derived from longitudinal analyses that quantifiably assess relationships between specific biomarkers and clinical measures of disease severity may ultimately help inform power calculations and dose-response modeling during early-phase trial design. Taken together, these findings suggest a role for specific serum biomarkers across multiple stages of the clinical research process.

This study is limited by its retrospective nature and small sample-size; larger prospective studies must validate our findings before they can be applied in clinical research settings more broadly. Nevertheless, this study provides a strong foundation for integrating objective biomarkers into the broader framework of HS research and, pending further validation, may ultimately support more rigorous and reproducible approaches to disease monitoring and treatment evaluation moving forward.

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**TABLE 1.**

**Baseline Demographic and Clinical Characteristics of Patients With Hidradenitis Suppurativa (HS)**

| Patient Characteristics | |
|---|---|
| Age at Diagnosis (N = 128) | 35.46 (13.52) |
| BMI (N = 123) | 33.76 (7.86) |
| Sex (N = 128) | |
| Male | 42 (33.81) |
| Female | 85 (66.41) |
| Other | 1 (0.78) |
| Race (N = 128) | |
| White | 15 (11.72) |
| Black | 63 (49.22) |
| Asian | 2 (1.56) |
| Other/Unknown | 48 (37.5) |
| Ethnicity (N = 128) | |
| Not Hispanic/Latino | 67 (52.34) |
| Hispanic/Latino | 46 (36.72) |
| Unknown | 14 (10.94) |
| FST (N = 73) | |
| II | 5 (6.85) |
| III | 11 (15.07) |
| IV | 17 (23.29) |
| V | 31 (42.47) |
| VI | 9 (12.33) |
| Insurance (N = 128) | |
| Medicare/Medicaid | 60 (46.88) |
| Commericial | 65 (50.78) |
| Uninsured | 3 (2.34) |
| Language (N = 128) | |
| English | 122 (95.31) |
| Spanish | 6 (4.69) |
| Smoking History (N = 128) | |
| Never | 81 (63.28) |
| Active | 17 (13.28) |
| Former | 30 (23.44) |
| Comorbidities | |
| T2DM (N = 128) | 27 (21.09) |
| Metabolic Syndrome (N = 128) | 13 (10.16) |
| PCOS (N = 128) | 13 (10.16) |
| IBD (N = 128) | 2 (1.56) |
| Iron Supplementation (N = 128) | 10 (7.87) |
| Disease Severity | |
| HS-PGA (1-6) (N = 128) | 3.27 (1.33) |
| NRS-Pain (0-10) (N = 127) | 3.90 (3.45) |
| Laboratory Markers | |
| Leukocytes (k/uL) (N = 128) | 10.0 (3.65) |
| HGB (g/dL) (N = 128) | 12.16 (1.93) |
| HCT (N = 128) | 38.79 (5.23) |
| MCV (fL) (N = 128) | 85.41 (7.66) |
| CRP (mg/dL) (N = 128) | 3.03 (3.50) |
| ESR (mm/h) (N = 127) | 60.32 (37.04) |
| IL-6 (pg/mL) (N = 68) | 33.30 (115.73) |
| Visit Characteristics (N = 1259) | Median (IQR) |
| Visits Per Patient | 8 (6) |
| Time Between Visits (days) | 70 (84) |
| Follow-Up Duration (days) | 878 (695) |

Continuous variables are presented as mean (standard deviation), and categorical variables as counts (percentages), unless otherwise specified. Reported averages for clinical and laboratory markers include data from intake visit only to represent baseline disease severity of the cohort. Reported averages for longitudinal measures (visits per patient, time between visits, follow-up duration) include data from all visits. BMI, body mass index; FST, Fitzpatrick skin type; T2DM, type II diabetes mellitus; PCOS, polycystic ovarian syndrome; HS-PGA, Hidradenitis Suppurativa-Physician Global Assessment; NRS-pain, Numerical Rating Scale for pain; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; STD, standard deviation.

**TABLE 2.**

**Longitudinal Associations Between Inflammatory Markers and Clinical Disease Severity in a Cohort of patients With Hidradenitis Suppurativa.**

| Predictor | β | Standard Error | t-value | *P*-value |
|---|---|---|---|---|
| Leukocytes | 0.029 | 0.006 | 4.556 | <0.001 |
| HGB | -0.161 | 0.017 | -9.659 | <0.001 |
| HCT | -0.053 | 0.007 | -7.775 | <0.001 |
| MCV | -0.018 | 0.004 | -4.684 | <0.001 |
| CRP | 0.144 | 0.012 | 12.425 | <0.001 |
| ESR | 0.012 | 0.001 | 12.228 | <0.001 |
| IL-6 | 0.005 | 0.001 | 5.933 | <0.001 |

Results of a linear mixed-effects model evaluating the association between clinical and laboratory predictors and HS-PGA score (n=128 patients). Subject was included as a random intercept to account for multiple visits per patient. Reported are standardized regression coefficients (β), standard errors, t-values, and *P*-values. HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6.

## DISCLOSURES

The authors have no conflict of interest to declare.

**IRB approval status:** Reviewed and approved by Einstein IRB (#2024-15978)

## REFERENCES

1. Andriano TM, Benesh G, Babbush KM, et al. Serum inflammatory markers and leukocyte profiles accurately describe hidradenitis suppurativa disease severity. *Int J Dermatol.* 2022;61(10):1270-1275.
2. Verma KK, Friedmann DP, Deligonul FZ, et al. Hidradenitis suppurativa prevalence by age and race in the United States. *J Dermatol Dermatol Surg.* 2024;28(2):105-107.
3. Gambichler T, Hessam S, Cramer P, et al. Complete blood collection-based systemic inflammation biomarkers for patients with hidradenitis suppurativa. *Acad Dermatol Venereol.* 2022;36(9):1593-1596.
4. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422-434.
5. Kimball AB, Jemec GBE, Alavi A, et al. Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. *Lancet.* 2023;401(10378):747-761.

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LETTERS TO THE EDITOR

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# Hidradenitis Suppurativa Increases Risk of Postoperative Complications After Mohs Surgery: A Retrospective Cohort Study

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*To the Editor,*

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by painful nodules, abscesses, and sinus tracts.[1] Though HS primarily affects intertriginous areas, it may involve the mandible, post-auricular area, scalp, temples, and nuchal skin.[1] Previous studies in orthopedic literature have demonstrated that patients with HS are at increased risk for adverse postoperative events, including wound dehiscence and surgical site infection.[2] Mohs micrographic surgery (MMS) is frequently performed to treat nonmelanoma skin cancer (NMSC) and melanoma (MM), particularly of the head and neck.[3] However, large-scale, real-world data assessing postoperative complications of MMS in patients with HS remains limited.

In this retrospective cohort study using the TriNetX Research Network, we evaluated whether HS is associated with increased postoperative complication rates in patients undergoing MMS for NMSC or MM. Patients with HS were identified using the ICD-10-CM for HS (L73.2). Patients with conditions impairing wound healing (epidermolysis bullosa, systemic sclerosis, Ehlers-Danlos, or Marfan syndrome), a history of postoperative complications prior to the study period, or systemic infection on the day of MMS were excluded. Patients with HS were propensity score matched on age, demographics, immunosuppressive medications, and comorbidities to a comparator cohort without HS. Postoperative complications were evaluated at 30 and 90 days following MMS with risk ratios (RR) and 95% confidence intervals (CI). Statistical significance was set at a two-tailed *P*-value <0.05.

One thousand forty-six (1,046) patients with HS were compared to 1,046 matched controls without HS (Table 1). At 30 days postoperatively, patients with HS were at a significantly increased risk of postoperative infection (RR 2.56, *P*=0.0026), delayed wound healing (RR 2.24, *P*=0.012), and dehiscence (RR 2.51, *P*=0.0047). At 90 days postoperatively, patients with HS remained at a significantly increased risk of postoperative infection (RR 2.17, *P*=0.003), delayed wound healing (RR 2.13, *P*=0.0098), and dehiscence (RR 2.13, *P*=0.0077). Our results suggest that HS is associated with postoperative infection, delayed wound healing, and dehiscence following MMS.

The pathophysiologic mechanism underlying these adverse outcomes likely involves the chronic inflammatory microenvironment in HS, which is characterized by bacterial dysbiosis and persistent colonization of open wounds and sinus tracts, serving as a reservoir for infection and delayed healing.[4] Beyond local manifestations, HS involves systemic immune dysregulation that may predispose patients to postoperative complications. Dysregulation of SOX9, a transcription factor essential for epithelial stem cell differentiation in wound repair, alongside elevated TNF-α and IL-17 activity and CXCL12/13-expressing fibroblasts, likely promote chronic inflammation and impaired healing.[5]

Limitations of our study include reliance on ICD-10-CM coding, retrospective design, and lack of clinical information on HS location, Hurley stage, perioperative antibiotic use, defect size, or repair type. Future prospective studies should clarify causality and inform targeted risk mitigation strategies.

## DISCLOSURES

SNT is an investigator/speaker for Bioventus, Kerecis, Boehringer Ingelheim, Regeneron, and CASTLE. Other authors have no relevant COI to declare.

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

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**TABLE 1.**

**Baseline Demographic Characteristics of the Celecoxib, Sirolimus, and Acitretin Cohorts After Propensity Score Matching (PSM)**

| Outcomes | HS Cohort | No HS Cohort | | | HS Cohort | No HS Cohort | | |
|---|---|---|---|---|---|---|---|---|
| | Number of eligible individuals (number of outcomes, 30-day) | Number of eligible individuals (number of outcomes, 30-day) | Risk Ratio (95% CI) | *P*-value | Number of eligible individuals (number of outcomes, 90-day) | Number of eligible individuals (number of outcomes, 90-day) | Risk Ratio (95% CI) | *P*-value |
| Postoperative infection | 1000 (33) | 1007 (13) | 2.56 (1.35-4.83) | 0.0026 | 1000 (43) | 1007 (20) | 2.17 (1.28-3.65) | 0.003 |
| Postoperative bleeding | 1020 (≤10) | 1029 (≤10) | N/A | N/A | 1020 (≤10) | 1029 (≤10) | N/A | N/A |
| Hematoma | 1020 (≤10) | 1029 (≤10) | N/A | N/A | 1020 (12) | 1029 (≤10) | N/A | N/A |
| Delayed wound healing | 1021 (29) | 1023 (13) | 2.24 (1.17-4.27) | 0.012 | 1021 (34) | 1023 (16) | 2.13 (1.18-3.83) | 0.0098 |
| Dehiscence | 1022 (30) | 1028 (12) | 2.51 (1.29-4.88) | 0.0047 | 1022 (36) | 1028 (17) | 2.13 (1.20-3.77) | 0.0077 |

**Ethics Statement:** Written informed consent from patients was not required as information from TriNetX is deidentified.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

## REFERENCES

1. Francois K, Moon HS, Panchal N. Cervicofacial hidradenitis suppurativa: A case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2023;135(2):e25-e31.
2. Gouzoulis MJ, Kammien AJ, Caruana DL, et al. Hidradenitis suppurativa leads to increased risk of wound-related complications following total joint arthroplasty. *Arthroplast Today.* 2022;16:169-174.
3. Tolkachjov SN, Brodland DG, Coldiron BM, et al. Understanding mohs micrographic surgery: a review and practical guide for the nondermatologist. *Mayo Clin Proc.* 2017;92(8):1261-1271.
4. Büyükaşik O, Hasdemir AO, Kahramansoy N, et al. Surgical approach to extensive hidradenitis suppurativa. Dermatol Surg. 2011;37(6):835-842.
5. Frew JW. Unravelling the complex pathogenesis of hidradenitis suppurativa. *Br J Dermatol.* 2025;192(Supplement_1):i3-i14.

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FEATURED CONTENT
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# NEWS, VIEWS, AND REVIEWS

## Beyond the Brain: Understanding the Dermatologic Associations of Neurodegenerative Diseases

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### INTRODUCTION

Neurodegenerative disorders are a prevalent cause of morbidity, often carrying substantial physical and psychosocial burden. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders, and both have manifestations that extend beyond the nervous system.[1] Emerging evidence has identified possible inflammatory, genetic, and biologic mechanisms linking PD and AD to a range of dermatologic diseases. Awareness of associations between cutaneous and neurologic disorders may help physicians recognize comorbid skin disease and inform dermatologic care for patients with mobility or cognitive challenges. This review explores the relationship between neurodegenerative disorders and the skin, highlighting possible mechanisms and practical considerations for dermatologists caring for patients with neurologic disease.

### Parkinson's Disease

PD occurs due to the progressive loss of dopaminergic neurons in the substantia nigra, resulting in motor symptoms such as resting tremor, bradykinesia, and shuffling-like gait.[1] A hallmark of PD is the abnormal accumulation of phosphorylated alpha-synuclein proteins. Phosphorylated alpha-synuclein can deposit in the brainstem, contributing to the motor symptoms observed in PD. This protein is also believed to deposit in peripheral cutaneous nerve fibers.[2] A growing body of literature is emerging in favor of using skin biopsies to support the diagnostic evaluation of PD, as opposed to solely relying on clinical observation and symptoms.[3] Punch biopsies of the skin have demonstrated high sensitivity and specificity for detecting the presence of phosphorylated alpha-synuclein.[2] A recent multi-center study demonstrated that 92.7% of participants with PD tested positive for phosphorylated alpha-synuclein on skin biopsy vs only 3.3% of control participants.[4] Dermatologists may therefore play a collaborative role in supporting neurology colleagues when diagnosing PD.

Additionally, a potential bidirectional relationship has been proposed between PD and cutaneous melanoma. A recent retrospective cohort study demonstrated that veterans with melanoma had a 47% higher risk of PD compared to veterans without melanoma (adjusted HR 1.47; CI 1.37-1.57).[5] Conversely, a cohort study with 333,990 participants found that males over age 65 with PD had a 2.8 times higher risk than those without PD to develop melanoma (HR 2.825; CI 1.395-5.721).[6] Several mechanisms have been theorized to support this relationship, though current understanding remains inconclusive.[7] One proposed theory suggests that alpha-synuclein can interfere with activation of tyrosinase, a key enzyme in melanogenesis. Suppression of tyrosinase activity can potentially increase the skin's susceptibility to ultraviolet-induced DNA damage.[7] Other theories have implicated levodopa, a medication used in the management of PD that also serves as a precursor in melanogenesis. Although the shared role of levodopa in melanin synthesis and the treatment of PD has prompted hypotheses, current evidence does not identify levodopa as a driving factor of melanoma.[7] However, given the relationship between PD and melanoma, the American Parkinson Disease Association recommends annual skin checks for patients with PD.[8]

Seborrheic dermatitis is also commonly associated with PD, affecting an estimated 18% to 59% of patients with PD as compared to roughly 4% of the general population.[9] Interestingly, seborrheic dermatitis may precede the diagnosis of PD. A retrospective case-control study identified an increased association between seborrheic dermatitis and PD up to 15 years before PD diagnosis (OR 1.47; CI 1.43-1.51). Alpha-synuclein has been proposed as a potential link for these conditions. Alpha-synuclein can accumulate in peripheral autonomic nerve fibers, which also innervate the sebaceous glands. Dysfunction of these fibers due to alpha-synuclein accumulation may alter sebum production, creating a favorable environment for the development of seborrheic dermatitis.[9]

### Alzheimer's Disease

AD is characterized by progressive memory loss and executive dysfunction due to an aberrant accumulation of amyloid plaques and neurofibrillary tangles within the brain.[1] AD has been associated with psoriasis, with a cohort study revealing that subjects with psoriasis had a 13% higher incidence of AD than subjects without psoriasis (HR 1.13; CI 1.10-1.16).[10] However, a clear relationship between the conditions has not been established. Inflammatory signaling has been proposed as a shared mechanism, with a study conducted in mice with transgenic AD demonstrating decreased cerebral amyloid following inhibition of IL-12 and IL-23 signaling. Inhibition of IL-12 and IL-23 signaling is also a key tenet of psoriasis treatment, suggesting potential for a shared inflammatory pathway between the conditions.[11] Genetic overlap may also contribute to this connection, with a genome-wide association study revealing a shared single nucleotide polymorphism near the HLA-DRB5 gene.[12] Further evidence is necessary to elucidate a pathophysiologic relationship between psoriasis and AD.

AD has also been associated with bullous pemphigoid (BP), with a meta-analysis demonstrating an increased risk of all forms of dementia in patients with BP (HR 1.41; CI 1.20-1.66).[13] In patients over the age of 80, those with BP had 40% higher odds of AD compared to those without BP (adjusted OR 1.40; CI 1.10-1.78).[14] While no mechanistic link has been identified between AD and BP, researchers have proposed a cross-reactive autoimmune response to the epidermal adhesion molecules BP180 and BP230. BP180 and BP230 are the targets of autoimmune activity in BP, and homologues of these proteins have been identified as present within the nervous system. However, the evidence supporting this postulated mechanism remains conflicting, warranting further investigation.[14]

**Practical Considerations**

The overlap between dermatologic and neurologic conditions has important implications for interdisciplinary care. From a neurology standpoint, awareness of the cutaneous associations of neurodegenerative diseases can allow for prompt recognition and referral to dermatology for appropriate management. From a dermatology standpoint, it is crucial to be mindful of mobility and cognitive status when working with patients who have PD and AD, respectively.

When working with patients with neurodegenerative disorders, it can be helpful to assess their ability to complete self-skin examinations at home. If conducting self-examinations is of concern, increasing the frequency of dermatology visits may be considered based on shared decision-making between the patient and provider.[15] Additionally, if topical medications are prescribed for patients with movement disorders, it is important to assess the ability of the patient to reach affected areas. If application of topical treatments presents a challenge, oral medications should be more strongly considered if appropriate.[15] Dermatologists should also be cognizant of the complexity of medication regimens when working with patients experiencing dementia. Close collaboration between dermatologists, patients, and their caregivers is crucial to establish an effective and manageable care plan.[16]

**Future Directions**

PD and AD have meaningful cutaneous manifestations that warrant awareness from both neurologists and dermatologists. While the relationship between neurodegenerative disorders and associated skin conditions has been well characterized by epidemiologic data, emerging research continues to identify potential pathophysiologic connections. Thus, additional studies should investigate possible underlying mechanisms and employ longitudinal, prospective designs to clarify directionality and causality of these associations. Establishing a deeper understanding of the overlap between neurodegenerative and dermatologic conditions can help inform screening guidelines, identify therapeutic targets, and facilitate streamlined interdisciplinary management for patients.

**DISCLOSURES**

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**REFERENCES**

1. Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harb Perspect Biol.* 2018;10(4):a033118. doi:10.1101/cshperspect.a033118
2. Agin-Liebes J, Lodge A, Reddy H, et al. α-synuclein biomarker assays: bridging research and patient care. *Lancet Neurol.* 2025;24(8):681-697. doi:10.1016/S1474-4422(25)00194-2
3. Isaacson JR, Freeman R, Gibbons CH. Clinical utility of synuclein skin biopsy in the diagnosis and evaluation of synucleinopathies. *Front Neurol.* 2024;15:1510796. doi:10.3389/fneur.2024.1510796
4. Gibbons CH, Levine T, Adler C, et al. Skin biopsy detection of phosphorylated α-synuclein in patients with synucleinopathies. *JAMA.* 2024;331(15):1298-1306. doi:10.1001/jama.2024.0792
5. Huhmann LB, Hwang JC, Perez D, et al. A retrospective cohort study using the Veterans Affairs Cancer Registry database: increased hazard of Parkinson's disease in United States veterans with melanoma. *J Am Acad Dermatol.* Published online August 27, 2026. doi:10.1016/j.jaad.2026.08.078
6. Ryu HJ, Park JH, Choi M, et al. Parkinson's disease and skin cancer risk: a nationwide population-based cohort study in Korea. *J Eur Acad Dermatol Venereol.* 2020;34(12):2775-2780. doi:10.1111/jdv.16462
7. Niemann N, Billnitzer A, Jankovic J. Parkinson's disease and skin. *Parkinsonism Relat Disord.* 2021;82:61-76. doi:10.1016/j.parkreldis.2020.11.017
8. American Parkinson Disease Association. Parkinson's disease and cancer: what's the connection? Available at: https://www.apdaparkinson.org/article/cancer-and-parkinsons-disease/. Accessed September 21, 2026.
9. Kefala V, Oikonomou E, Sfyri E, et al. Genetic, lipid, fungal microbiome and neuroinflammatory links between seborrheic dermatitis and Parkinson's disease: a narrative review. *Genes (Basel).* 2026;17(8):894. doi:10.3390/genes17080894
10. Huang J, Su B, Karhunen V, et al. Inflammatory diseases, inflammatory biomarkers, and Alzheimer disease: an observational analysis and Mendelian randomization. *Neurology.* 2023;100(6):e568-e581. doi:10.1212/WNL.0000000000201489
11. vom Berg J, Prokop S, Miller K, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease–like pathology and cognitive decline. *Nat Med.* 2012;18:1812–1819. doi:10.1038/nm.2965
12. Yokoyama JS, Wang Y, Schork AJ, et al. Association between genetic traits for immune-mediated diseases and Alzheimer disease. *JAMA Neurol.* 2016;73(6):691-697. doi:10.1001/jamaneurol.2016.0150
13. Zhou Q, Xiong Z, Yang D, et al. The association between bullous pemphigoid and cognitive outcomes in middle-aged and older adults: A systematic review and meta-analysis. *PLoS One.* 2023;18(11):e0295135. doi: 10.1371/journal.pone.0295135
14. Xie Z, Gao Y, Tian L, et al. Pemphigus and pemphigoid are associated with Alzheimer's disease in older adults: evidence from the US Nationwide Inpatient Sample 2016–2018. *BMC Geriatr.* 2023;23:872. doi:10.1186/s12877-023-04580-z
15. Nassim JS, Watson AJ, Tan JK. Achieving equitable care for people with disabilities: considerations for the dermatologist. *JAMA Dermatol.* 2020;156(11):1173-1175. doi:10.1001/jamadermatol.2020.3955
16. Cardona-Arango D, Santacruz-Restrepo V, Rendón-Montoya A, et al. Medication adherence in older adults with chronic diseases: a scoping review of barriers, facilitators, and effective interventions. *Front Aging.* 2026;7:1642652. doi:10.3389/fragi.2026.1642652

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*28-day clinical study with 3-day relapse period.
†Due to dryness. Consumer study on 139 subjects presenting itch sensations due to dryness. Result 24 hours after stopping product use following 15 days of product application once a day.
‡50 adults with pruritic dermatosis including atopic dermatitis (n=16) applied Lipikar AP+Max twice daily for 4 weeks.

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§Do not use on broken skin. Consult a medical professional prior to use. La Roche-Posay ribbon is not affiliated with any organization.

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