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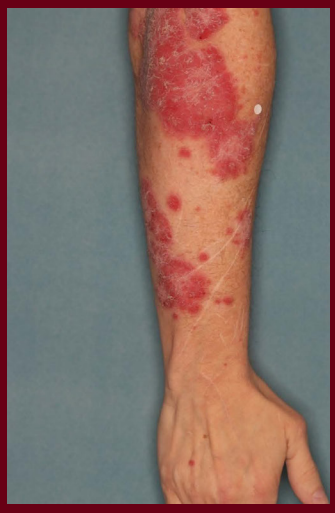

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SPECIAL FOCUS: PSORIASIS

RESIDENT ROUNDS ◆ NEWS, VIEWS, & REVIEWS ◆ PIPELINE PREVIEWS ◆ CLINICAL TRIAL REVIEW

ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

Skyrizi®
risankizumab-rzaa

#1
PRESCRIBED BIOLOGIC
BY DERMATOLOGISTS FOR PATIENTS WITH PSORIATIC DISEASE

#1 PRESCRIPTION ANALYSIS CALCULATED BY COMBINED PRESCRIPTION DATA ACROSS Ps AND PsA

For patients with psoriatic disease, defined as those with plaque psoriasis or psoriatic arthritis. Source of data: Integrated Symphony Health (PatientSource) as of 8/2022.[1]

An IL-23 inhibitor for adults with moderate to severe plaque psoriasis (Ps) and for adults with active psoriatic arthritis (PsA)[2]

NOTHING IS EVERYTHING

Nothing less than the opportunity to reach for their treatment goals.
For your patients, that's everything.

UltIMMa-1 & 2 STUDY DESIGN[3]

UltIMMa-1 (N=506) and **UltIMMa-2** (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and 16, and every 12 weeks thereafter. Co-primary endpoints were PASI 90 and sPGA 0/1 at Week 16 vs placebo in each study (assessed by non-responder imputation).

KEEPsAKE-1 & 2 STUDY DESIGN[2,4,5]

KEEPsAKE-1 and **KEEPsAKE-2** were phase 3, multicenter, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of SKYRIZI in adults with active PsA. **KEEPsAKE-1** included patients who had an inadequate response or intolerance to at least 1 DMARD. **KEEPsAKE-2** included patients who had an inadequate response or intolerance to biologic therapy and/or DMARDs (mixed population of bio-naïve and bio-experienced). Patients were randomized to SKYRIZI 150 mg or placebo followed by SKYRIZI 150 mg at Week 28. The primary endpoint for both studies was the proportion of patients who achieved ACR20 at Week 24.

ACR20=American College of Rheumatology 20% improvement criteria; DMARD=Disease-Modifying Antirheumatic Drug.

abbvie

 US-SKZD-230086 April 2023

SKYRIZI GIVES YOUR PATIENTS THE OPPORTUNITY FOR...

DURABLE, RAPID & CLEAR SKIN

In **Ps**, most patients achieved co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16, including response 4 weeks after 1st dose. Most patients who achieved PASI 90 at Week 16 maintained it at Week 52.[2,3]

PASI 100 was achieved by many patients at Week 16 and by a majority at Week 52.[2]

POWERFUL JOINT SYMPTOM RELIEF

In **PsA**, a majority of patients achieved the primary endpoint of ACR20 at Week 24, experiencing improvement in joint symptoms including patient-reported pain data.[2]

4 INJECTIONS A YEAR

Reliable quarterly dosing after 2 initiation doses at Weeks 0 and 4 (150 mg/dose) for **Ps** and **PsA**.[2]

Safety data up to ~8 years in Ps clinical trials and ~3 years in PsA clinical trials.
Safety profile observed in PsA is generally consistent to Ps (PsA Week 24, Ps Week 16).[2,6,7]

LEARN MORE AT SKYRIZIHCP.COM

INDICATIONS[2]

Plaque Psoriasis: SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis: SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

IMPORTANT SAFETY INFORMATION[2]

Hypersensitivity Reactions

SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately.

Infection

SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Tuberculosis (TB)

Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines.

Adverse Reactions

Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

In psoriatic arthritis phase 3 trials, the incidence of hepatic events was higher with SKYRIZI compared to placebo.

SKYRIZI is available in a 150 mg/mL prefilled syringe and pen.

Please see the Brief Summary of the Full Prescribing Information on the following page.

References: 1. Data on file, AbbVie Inc. PatientSource/IQVIA data. 2022. **2.** SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **3.** Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661. **4.** Kristensen LE, Papp K, White D, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 100-week results from the KEEPsAKE 1 and KEEPsAKE 2 trials. Poster presented at: American College of Rheumatology Convergence; November 10-14, 2022; Philadelphia, Pennsylvania. **5.** Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann Rheum Dis*. 2022;81(2):225-231. **6.** Gordon KB, Blauvelt A, Coates LC, et al. Risankizumab long-term safety in patients with psoriatic disease: integrated analyses of data from psoriasis and psoriatic arthritis clinical trials. Poster presented at: 31st Congress of the European Academy of Dermatology and Venerology (EADV 2022); September 7-10, 2022; Milan, Italy. **7.** Data on file, ABVRRTI73417. AbbVie Inc.

SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous or intravenous use

150 mg/mL single-dose pen and prefilled syringe
600 mg/10 mL single-dose vial for intravenous infusion
180 mg/1.2 mL single-dose prefilled cartridge with on-body injector
360 mg/2.4 mL single-dose prefilled cartridge with on-body injector

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Plaque Psoriasis

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis

SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Crohn's Disease

SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately *[see Adverse Reactions]*.

Infections

SKYRIZI may increase the risk of infections *[see Adverse Reactions]*.

Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the PsO-3 study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity in Treatment of Crohn's Disease

A serious adverse reaction of drug-induced liver injury in conjunction with a rash that required hospitalization was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two 600 mg intravenous doses of SKYRIZI. The liver test abnormalities resolved following administration of steroids. SKYRIZI was subsequently discontinued.

For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline, and during induction at least up to 12 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Tuberculosis *[see Warnings and Precautions]*
- Hepatotoxicity in Treatment of Crohn's Disease *[see Warnings and Precautions]*

Clinical Trials Experience

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

Plaque Psoriasis

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In Studies PsO-1 and PsO-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Psoriatic Arthritis

The overall safety profile observed in subjects with psoriatic arthritis treated with SKYRIZI is generally consistent with the safety profile in subjects with plaque psoriasis. Additionally, in the Phase 3 placebo-controlled trials the incidence of hepatic events was higher in the SKYRIZI group (5.4%, 16.7 events per 100 patient years) compared to the placebo group (3.9%, 12.6 events per 100 patient years). Of these, the most common events that were reported more frequently in both the placebo group and the SKYRIZI group were ALT increased (placebo: n=12 (1.7%); SKYRIZI: n=16 (2.3%)), AST increased (placebo: n=9 (1.3%); SKYRIZI: n=13 (1.8%)), and GGT increased (placebo: n=5 (0.7%); SKYRIZI: n=8 (1.1%)). There were no serious hepatic events reported. The incidence of hypersensitivity reactions was higher in the SKYRIZI group (n=16, 2.3%) compared to the placebo group (n=9, 1.3%). In the Phase 3 placebo-controlled trials, hypersensitivity reactions reported at a higher rate in the SKYRIZI group included rash (placebo: n=4 (0.6%); SKYRIZI: n=5 (0.7%), allergic rhinitis (placebo: n=1 (0.1%); SKYRIZI: n=2 (0.3%), and facial swelling (placebo: n=0 (0.0%); SKYRIZI n=1 (0.1%). One case of anaphylaxis was reported in a subject who received SKYRIZI in the Phase 2 clinical trial.

Crohn's Disease

SKYRIZI was studied up to 12 weeks in subjects with moderately to severely active Crohn's disease in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2) and a randomized, double-blind, placebo-controlled, dose-finding study (CD-4; NCT02031276). Long-term safety up to 52 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3).

In the two induction studies (CD-1, CD-2) and the dose finding study (CD-4), 620 subjects received the SKYRIZI intravenous induction regimen at Weeks 0, 4 and 8. In the maintenance study (CD-3), 297 subjects who achieved clinical response, defined as a reduction in CDAI of at least 100 points from baseline after 12 weeks of induction treatment with intravenous SKYRIZI in studies CD-1 and CD-2, received a maintenance regimen of SKYRIZI either 180 mg or 360 mg subcutaneously at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks.

Adverse reactions reported in > 3% of subjects in induction studies and at a higher rate than placebo are shown in Table 2.

Table 2. Adverse Drug Reactions Reported in > 3% of Subjects with Crohn's Disease Treated with SKYRIZI in Placebo-Controlled 12-Week Induction Studies

Adverse Drug Reactions	SKYRIZI 600 mg Intravenous Infusion[a] N = 620 n (%)	Placebo N = 432 n (%)
Upper respiratory infections[b]	66 (10.6)	40 (9.3)
Headache[c]	41 (6.6)	24 (5.6)
Arthralgia	31 (5.0)	19 (4.4)

[a] SKYRIZI 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8.
[b] Includes: influenza like illness, nasopharyngitis, influenza, pharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, COVID-19, nasal congestion, respiratory tract infection viral, viral pharyngitis, tonsillitis, upper respiratory tract inflammation
[c] Includes: headache, tension headache

Adverse reactions reported in >3% of subjects in the maintenance study and at a higher rate than placebo are shown in Table 3.

Table 3. Adverse Reactions Reported in >3% of Subjects with Crohn's Disease Treated with SKYRIZI[a] in Placebo-Controlled 52-Week Maintenance Study (CD-3)

Adverse Drug Reactions	SKYRIZI 180 mg Subcutaneous Injection N = 155 n (%)	SKYRIZI 360 mg Subcutaneous Injection N = 142 n (%)	Placebo N = 143 n (%)
Arthralgia	13 (8.4)	13 (9.2)	12 (8.4)
Abdominal pain[b]	9 (5.8)	12 (8.5)	6 (4.2)
Injection site reactions[c,d]	7 (4.5)	8 (5.6)	4 (2.8)
Anemia	7 (4.5)	7 (4.9)	6 (4.2)
Pyrexia	4 (2.6)	7 (4.9)	4 (2.8)
Back pain	3 (1.9)	6 (4.2)	3 (2.1)
Arthropathy	1 (0.6)	5 (3.5)	2 (1.4)
Urinary tract infection	1 (0.6)	5 (3.5)	4 (2.8)

[a] SKYRIZI 180 mg or 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks
[b] Includes: abdominal pain, abdominal pain upper, abdominal pain lower
[c] Includes: injection site rash, injection site erythema, injection site swelling, injection site urticaria, injection site warmth, injection site pain, injection site hypersensitivity, injection site reaction
[d] Some subjects had multiple occurrences of injection site reactions. In this table, injection site reactions are counted only once per subject for the rate calculations.

Specific Adverse Drug Reactions

Infections

In the maintenance study (CD-3) through Week 52, the rate of infections was 32.3% (50.2 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 36.6% (60.8 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 36.4% (60.3 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction. The rate of serious infections was 2.6% (2.7 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 5.6% (7.4 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 2.1% (2.4 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction.

Lipid Elevations

Elevations in lipid parameters (total cholesterol and low-density lipoprotein cholesterol [LDL-C]) were first assessed at 4 weeks following initiation of SKYRIZI in the induction trials (CD-1, CD-2). Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12. Following SKYRIZI induction, mean total cholesterol increased by 9.4 mg/dL from baseline to a mean absolute value of 175.1 mg/dL at Week 12. Similarly, mean LDL-C increased by 6.6 mg/dL from baseline to a mean absolute value of 92.6 mg/dL at Week 12. Mean LDL-C increased by 3.1 mg/dL from baseline to a mean absolute value of 99.0 mg/dL at Week 52 with SKYRIZI 180 mg maintenance treatment and by 2.3 mg/dL from baseline to a mean absolute value of 102.2 mg/dL at Week 52 with SKYRIZI 360 mg maintenance treatment.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

Plaque Psoriasis

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had

antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

Crohn's Disease

By Week 64, antibodies to risankizumab-rzaa developed in approximately 3.4% (2/58) of subjects treated with SKYRIZI induction followed by 360 mg maintenance regimen. No subjects (0/57) treated with SKYRIZI induction followed by 180 mg maintenance regimen developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing.

Postmarketing Experience

The following adverse reactions have been reported during post-approval of SKYRIZI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SKYRIZI exposure:

- *Skin and subcutaneous tissue disorders*: eczema and rash

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161 or visiting http://glowpregnancyregistry.com.

Risk Summary

Available pharmacovigilance and clinical trial data with risankizumab use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on risankizumab-rzaa, monoclonal antibodies can be actively transported across the placenta, and SKYRIZI may cause immunosuppression in the in utero-exposed infant. There are adverse pregnancy outcomes in women with inflammatory bowel disease *(see Clinical Considerations)*.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 or 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. Increased fetal/infant loss was noted in pregnant monkeys at the 50 mg/kg dose *(see Data)*. The 50 mg/kg dose in pregnant monkeys resulted in approximately 10 times the exposure (AUC) in humans administered the 600 mg induction regimen and 39 times the exposure (AUC) to the 360 mg maintenance doses, respectively. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal adverse reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because risankizumab may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to SKYRIZI in utero. There are insufficient data regarding infant serum levels of risankizumab at birth and the duration of persistence of risankizumab in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 5 months after birth should be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg and the NOAEL for developmental toxicity was identified as 5 mg/kg. On an exposure (AUC) basis, the 5 mg/kg dose in pregnant monkeys resulted in approximately 1.24 times the exposure in humans administered the 600 mg induction regimen and 5 times the exposure in humans administered the 360 mg maintenance doses, respectively. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17%-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to risankizumab-rzaa are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of SKYRIZI have not been established in pediatric patients.

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in SKYRIZI exposure, safety, or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

Clinical studies of SKYRIZI for the treatment of Crohn's disease did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of risankizumab-rzaa were observed in geriatric subjects compared to younger adult subjects with Crohn's disease.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions

Advise patients to discontinue SKYRIZI and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions]*.

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions]*.

Hepatotoxicity in Treatment of Crohn's Disease

Inform patients that SKYRIZI may cause liver injury, especially during the initial 12 weeks of treatment. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of liver dysfunction. (e.g., unexplained rash, nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) *[see Warnings and Precautions]*.

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI.

Instruct patients or caregivers in the technique of pen or syringe disposal.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to SKYRIZI during pregnancy *[see Use in Specific Populations]*.

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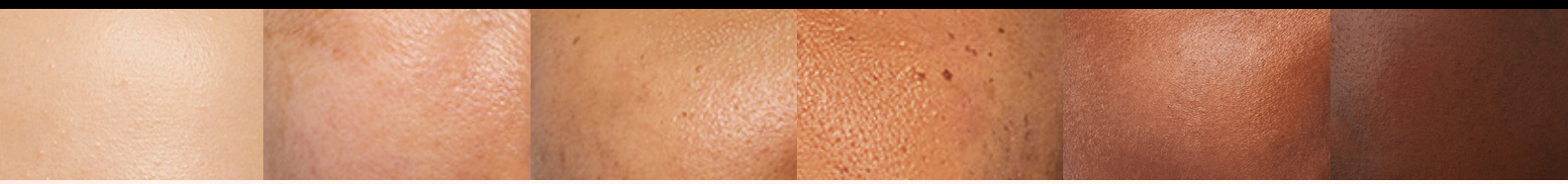

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ORIGINAL ARTICLE

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Consensus Statements on the Use of Corticosteroid-Containing Topical Medications in Psoriasis

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ABSTRACT

This article aims to provide consensus statements on the use of corticosteroid-containing topical medications for the management of psoriasis. This Psoriasis Expert Group (PEG) includes dermatologist voting members with expertise in psoriasis who convened and evaluated the use of topical medications and previously published guidelines. A modified Delphi process was conducted to reach consensus results. Two rounds of voting were conducted for each topic and panel consensus was determined.

Nine statements were developed regarding topical medication efficacy, patient quality of life, frequency of application, medication "feel", and safety and tolerability. Dermatologist experts voted on the statements separately. Patients were not polled. All items received agreement: 15 with high consensus and 1 with moderate consensus.

For the treatment of psoriasis, the PEG agreed that patients and physicians prefer topical medications that are effective, provide long-lasting results, have a quick onset of action, and "feel good on the skin" with few adverse effects. The developed consensus statements provide guidance on the topical treatment of psoriasis, including combination therapies, such as a vitamin D and topical corticosteroid analog. These recommendations will be continuously reviewed and updated as more evidence continues to emerge.

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INTRODUCTION

Topical corticosteroids (TCS) continue to be a mainstay of primary and/or adjunctive therapy for all severities of psoriasis. Corticosteroid-containing topical medications include both monotherapy and combination formulations with vitamin D or vitamin A derivatives. The American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) recently published joint guidelines on the use of topical therapies in psoriasis.[1] Since its publication, additional advancements in TCS have generated new evidence that requires evaluation and interpretation.

A group of dermatologists with expertise in the treatment of psoriasis gathered to evaluate current evidence on corticosteroid-containing topical medications and participated in a Delphi consensus process to generate statements that reflect the current state of evidence and help guide clinician decision-making. This Delphi consensus process aims to evaluate current evidence and generate consensus statements on the (1) speed of onset of action, (2) depth of response, (3) maintenance of effect, (4) patient's quality of life (QoL), (5) frequency of application, (6) "feel" of the medication on the skin, (7) application site reactions, (8) comparison of combination and monotherapy TCS, (9) for long-term side effects.

MATERIALS AND METHODS

A Psoriasis Expert Group (PEG) consisting of board-certified dermatologists with expertise in the topical treatment of psoriasis was convened. A narrative review of TCS-containing therapies was performed, including monotherapy and combination formulations with nonsteroidal analogs, such

as betamethasone dipropionate/calcipotriene (CAL/BDP) and halobetasol propionate (HP)/tazarotene (TAZ).

The PEG met in person to address 10 core consensus statements about topical therapies for the treatment of psoriasis. A modified Delphi process based on the RAND appropriateness method was used to establish new treatment recommendations. Participants voted on a scale of 1 to 9 for each consensus statement. Panel consensus was determined as: (1) high if all panelists' votes fell into a single tertile, (2) low if 25% or more votes fell in the 1 to 3 range with concurrent 25% or more votes in the 7 to 9 range, and (3) moderate for all other combinations. It was determined a priori that a maximum of 2 rounds of voting would be performed, and only 1 round of voting would be needed if a high consensus was achieved within the first round of voting. The voting results were analyzed by an independent scholar.

Expert Guidance Consensus Statements 1 to 9

Consensus Statement 1:

1a: Topical therapies with a faster onset of action are preferred by patients.

1b: Topical therapies with a faster onset of action are preferred by clinicians.

The degree of agreement with statement 1a is high. The degree of agreement with statement 1b is moderate. Patients may prefer treatments that result in rapid improvement of their psoriasis, allowing them to experience a faster normalization in their QoL and daily activities.[2] For example, CAL/BDP cream demonstrated improvement as early as week 1, and significant PGA treatment success by week 4 compared with CAL/BDP topical suspension (40.1% vs 24.0%, $P<0.0001$).[3] Those on CAL/BDP cream experienced a significantly higher improvement in QoL in comparison with those using the topical suspension (43.8% vs 34.2%, $P=0.0005$).[3]

In another study, combination CAL/BDP ointment resulted in significant reduction in Psoriasis Area and Severity Index (PASI) score as early as week 1 of treatment in comparison with CAL monotherapy or BDP alone ($P<0.001$).[4] A systematic review examining treatment preferences among 35,388 psoriasis patients demonstrated that patients preferred treatments with faster onset of action.[5] Thus, patients prefer treatments with faster onset of action that results in rapid improvement.

Consensus Statement 2:

2a: Topical therapies with higher efficacy are preferred by patients.

2b: Topical therapies with higher efficacy are preferred by clinicians.

The degree of agreement with statements 2a and 2b is high. Selecting treatments with maximal efficacy is important to patients so that they can achieve skin clearance and improve their QoL. For example, in a phase 3 randomized control trial (RCT), 43.2% of patients on CAL/BDP cream demonstrated significant Provider Global Assessment (PGA) treatment success over an 8-week treatment period in comparison with 31.9% of those on CAL/BDP topical suspension and 5.2% of those on vehicle ($P<0.001$).[3]

Furthermore, another phase 3 RCT showed a significant percentage reduction in mean PASI score from baseline by week 8 ($P<0.0001$) and significant itch reduction by week 4 ($P<0.01$) with CAL/BDP cream vs CAL/BDP topical suspension or vehicle.[6] CAL/BDP ointment demonstrated significant PGA treatment success after a 4-week treatment period, with 48.0% of subjects on CAL/BDP ointment experiencing absent or very mild disease in comparison with 16.5% of those on calcipotriene only and 26.3% of those on betamethasone dipropionate only.[7]

Furthermore, CAL/BDP ointment resulted in significant percentage reduction in PASI score as early as week 1 of treatment in comparison with CAL or BDP monotherapy ($P<0.001$).[5] Similarly, Kaufmann et al showed that 37% of patients on combination CAL/BDP ointment experienced treatment success, defined by mean reduction in PASI, in comparison with 22.3% in the CAL only group and 10.2% in the vehicle group ($P<0.001$).[8] Significantly more patients on CAL/BDP foam achieved PGA treatment success compared with those on CAL (45% vs 14.9%, $P<0.001$) or BDP foam (45% vs 30.7%, $P=0.047$).[9]

For scalp psoriasis, more patients achieved PGA treatment success with CAL/BDP vs CAL foam (53.0% vs 35.6%, $P=0.021$), but not those on BDP foam.[9] CAL/BDP foam also demonstrated significant reduction in mean mPASI score at the end of a 4-week treatment period vs CAL or BDP foam (71% vs 42% vs 55%) respectively, $P<0.003$ for PASI50 in both comparisons).[9] Thus, patients prefer treatments with excellent efficacy because they offer significant improvement in psoriasis.

Consensus Statement 3:

3a: Topical therapies with maintenance of effect and/or durability are preferred by patients.

3b: Topical therapies with maintenance of effect and/or durability are preferred by clinicians.

The degree of agreement with statements 3a and 3b is high. Patients experience more treatment satisfaction with psoriasis therapies that exhibit long-term efficacy. In the PSO-LONG Phase III RCT consisting of 545 patients, patients randomized to proactive treatment with CAL/BDP foam demonstrated an

additional 41 days of remission compared with the reactive group on vehicle (P<0.001).[10] In addition, the odds of response in mPASI75 and Dermatology Life Quality Index (DLQI) outcome measures were significantly higher for the proactive treatment group (P=0.0028, P=0.0025, respectively).[10]

Data on the long-term efficacy of CAL/BDP are limited. However, in long-term extension data from the PSOARING phase 3 RCT, the non-steroidal, aryl hydrocarbon receptor modulator tapinarof was associated with a remittive effect – defined as a PGA score of 0 (clear) or 1 (almost clear) off therapy for patients who were clear at the end of the placebo-controlled 12-week treatment period.[11] The median time to worsening of disease from complete clearance (PGA≥2) off therapy was 115 days off tapinarof therapy.[11] However, it is important to note the small sample size as a limitation of this study. In summary, the conclusions from these studies emphasize the importance of long-term durability and maintenance of treatment effect for both physicians and patients.

Consensus Statement 4:
Topical therapies that substantially improve patients' dermatology-related quality of life are preferred by patients.

The degree of agreement with statement 4 is high. Patients experience more treatment satisfaction with therapies that help them resume normal day-to-day activities. Data from a Phase III clinical trial showed that 43.8% of patients on CAL/BDP cream exhibited higher DLQI scores as early as week 4 (P=0.0002; continuing up to week 8) in comparison with only 34.2% of those on CAL/BDP topical suspension.[3] In the PSO-LONG phase 3 RCT, those treated with CAL/BDP foam also displayed significant improvement in DLQI scores (P=0.0025) in comparison with those on vehicle.[10] Thus, topical therapies that improve QoL and allow patients to resume normal activities are preferred by patients.

Consensus Statement 5:
5a: Topical therapies with less frequent application are preferred by patients.

5b: Topical therapies with less frequent application are preferred by clinicians.

The degree of agreement with statement 5a is high. The degree of agreement with statement 5b is moderate. Patients prefer less frequent application of topical therapies because this simplifies the treatment regimen and reduces patient's time for application. In a study evaluating the most important attributes of topical medications for psoriasis treatment using the PSO-TOPAP (Topical Attributes and Preferences) Questionnaire, 91% of patients cited a once-daily regimen as a very important attribute in medication selection.[10] In a systematic review of 22 studies examining data about psoriasis topical treatment adherence, 38% and 40% of patients in 2 separate studies deviated from the original written prescription due to desiring a lower frequency of application.[12] In areas outside of dermatology, adherence has also been found to be inversely related to dose frequency.[13] Therefore, topical treatments with a reduced number of application frequencies are desired by patients in dermatology.

Consensus Statement 6:
6a: Topical therapies that "feel good" on the skin are preferred by patients.

6b: Topical therapies that "feel good" on the skin are preferred by clinicians.

The degree of agreement with statements 6a and 6b is high. The cosmetic properties of a topical therapy are an important attribute that influence patient satisfaction and adherence. Topical medications are available in a wide variety of vehicles such as ointments, creams, gels, solutions, and foams, each with unique advantages and disadvantages. Ointments have occlusive properties that increase skin hydration and penetration but are greasy than other vehicles. Gels, on the other hand, dry as a greaseless non-occlusive film, but provide minimal skin hydration.

A systematic review of 12 studies evaluating psoriasis patient preferences for topical drug formulation found that, in general, patients prefer treatments that are easy to apply and less oily and messy.[14] In a survey of 449 psoriasis patients assessing experience in applying medication-free aerosol foam (identical to the vehicle used in CAL/BD aerosol foam), the aerosol foam vehicle was preferred over their current topical treatment vehicle by 4.5:1. Patients with poor disease control favored CAL/BD foam over their current treatment, likely because the foam vehicle is soothing on areas of active disease.

In PSO-Insightful, a study evaluating topical treatment attributes for CAL/BD foam and gel vs their most recent topical treatment, patients ranked Cal/BD aerosol foam significantly higher for "feeling soothing" and "providing immediate relief" (P<0.001 for both).[15] In RCT evaluating treatment convenience of CAL/BDP cream vs topical suspension based on ease of application, greasiness during and after treatment, treatment moisturization, and overall satisfaction, CAL/BDP demonstrated superiority in all categories, especially greasiness after treatment application.[2] Overall, these data suggest that patients prefer treatments that "feel good" on the skin in terms of greasiness and ease of application, which may lead to improved treatment adherence and efficacy.

Consensus Statement 7:

7a: Topical therapies that have lower rates of application site-related adverse events (example: contact dermatitis, irritant dermatitis, burning, and stinging) are preferred by patients.

7b: Topical therapies that have lower rates of application site-related adverse events (example: contact dermatitis, irritant dermatitis, burning, and stinging) are preferred by clinicians.

The degree of agreement with statements 7a and 7b is high. The probability of application site reactions is an important consideration for dermatologists when prescribing topical psoriasis therapies. In a study evaluating the efficacy of CAL/BDP, individuals using the combination therapy experienced fewer lesional/perilesional adverse reactions than patients on CAL monotherapy (9.9% vs 17.2%, P=0.008).[5] In a review evaluating the safety and efficacy of CAL/BDP in 6 large clinical trials, lesional and perilesional drug reactions occurred in up to 10.6% of those treated with CAL/BDP, with no significant difference between once- or twice-daily administration.[16] This frequency was similar to that reported in the BDP only group, and both were significantly lower than the CAL-only group.

The most common application site reaction for those on combination therapy was pruritus, which occurred in 2.6% to 5.1% of participants in these trials.[16] In a phase 3 randomized control trial of 796 patients evaluating CAL/BDP cream vs topical suspension and vehicle, the incidence of adverse events was similar across all groups. The most common application site-related adverse event reported by <1% of all participants treated with CAL/BDP cream was application-site irritation (1% cream vs 0% TS and vehicle).[17] The overall evidence suggests that the rates of application site adverse reactions are important to consider when prescribing topical therapies for psoriasis.

Consensus Statement 8:

In patients with plaque psoriasis, the benefit-risk profiles support the consideration of combination topical therapies (topical corticosteroid combined with a non-steroidal agent (such as topical vitamin D or a topical vitamin A) prior to topical steroid monotherapy.

The degree of agreement with statement 8 is high. Psoriasis patients prefer treatments that maximize improvement and minimize adverse event risk. CAL/BDP cream demonstrated significant improvement as early as week 1 of the treatment period compared with vehicle.[3] In addition, patients on CAL/BDP cream demonstrated significant PGA treatment success by week 4 in comparison with combination topical suspension (P<0.0001).[3]

A narrative review in 2017 examined all studies up until 2017 that evaluated the efficacy of combination therapy for psoriasis treatment in comparison with monotherapy with CAL or BDP.[18] Saraceno et al noted clinically statistical improvement (P<0.001) with the use of daily combination therapy for 4 weeks followed by 8 weeks of CAL monotherapy in comparison with CAL monotherapy alone.[19] Fleming et al demonstrated a significantly greater percentage of efficacy on combination therapy with 27.2% improved PGA score vs gel (0.0%) or monotherapy with CAL (11.4%) or BDP (16.9%).[18] In addition, Huang et al noted that subjects on once-daily combination therapy benefited from a greater decrease in PASI score after 4 weeks than those on CAL monotherapy twice daily.[18] A meta-analysis of 19 studies demonstrated significant improvement in PASI score for the 2-compound formulation vs CAL or BDP.[18]

Moreover, HP 0.01%/TAZ 0.045% lotion is associated with a lower risk of side effects compared with HP or TAZ monotherapy. For example, in the long term open-label study of HP/TAZ, in which participants received up to 24 weeks of continuous treatment with HP 0.01%/TAZ 0.045% lotion, peak incidence of skin atrophy was low (2.3% at week 8) and declined over the course of the study. In addition, atrophy was reported as an adverse event in only 4 participants (0.7%) and led to one discontinuation.[20] Overall, patients with psoriasis in non-intertriginous areas may benefit more from treatments with a favorable benefit-risk profile.

Consensus Statement 9:

9a: Topical therapies that have lower rates of long-term side effects (eg, skin thinning) are preferred by patients.

9b: Topical therapies that have lower rates of long-term side effects (eg, skin thinning) are preferred by clinicians.

The degree of agreement with statement 9a is moderate. The degree of agreement with statement 9b is high. Patients and physicians may prefer topical therapies with lower rates of long-term side effects so that they can use these therapies for longer periods of time over the course of their chronic disease. A prospective study identified that the risk of skin atrophy due to topical steroids was the second most important attribute that influences patients' preferences for topical therapies second to improvement on the topical therapy.[21]

In a study seeking to identify the educational needs regarding topical therapies for psoriasis, 30% of respondents asked questions regarding the side effect profile of medications, with a major emphasis on topical steroids in particular.[22] These studies highlight that many patients commonly express fears regarding the side effects of topical steroid therapy, and therefore consider it highly in their decision-making to include topical steroids as part of their psoriasis treatment. Several non-steroid topicals including CAL and TAZ have been used for psoriasis for years. New non-steroids including tapinarof and roflumilast are also

now approved for psoriasis. Roflumilast was specifically studied in intertriginous sites where use of topical steroids can lead development of striae.

DISCUSSION

Topical steroids remain the cornerstone of treatment for psoriasis. Advancements in the use of corticosteroid-containing topical therapies in psoriasis offer prompt evaluation and interpretation to help guide clinician decision-making.

Recommendations from the PEG reflect on the following topics: (1) speed of onset of action, (2) depth of response, (3) maintenance of effect, (4) patient's QoL, (5) frequency of application, (6) general "feel" on the skin, (7) application site reactions, (8) comparison with topical steroid monotherapy, and (9) long-term side effects.

The PEG encourages physicians to consider each patient's unique characteristics and therapeutic goals before prescribing a topical corticosteroid-containing agent for the treatment of a patients' psoriasis. Combination topical corticosteroid containing therapies are particularly helpful due to their improved side effect burden and maintenance of effect. Medications that are cosmetically elegant or "feel good on the skin" and require a low number of applications are also preferable for patients.

Ultimately, physicians should employ shared decision-making by participating jointly in health decisions with patients, discussing the benefits and risks of various treatment options, and considering the patient's preferences and circumstances to find the best individual treatment plan. Employing this model is helpful in the management of chronic diseases like psoriasis, which requires a relationship of lasting trust between the physician and patient.

DISCLOSURES

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Diagnosis and Management of Pediatric Psoriasis: An Overview for Pediatricians

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ABSTRACT

Pediatric psoriasis (PsO) and its associated comorbidities carry physical and psychosocial burdens in children and adolescents, which can negatively impact quality of life. However, features distinguishing pediatric PsO from eczema and other common inflammatory skin diseases may not be obvious to primary care providers, which may contribute to underrecognition and misdiagnosis. Accurate diagnosis of pediatric PsO is critical for managing the physical and psychological burdens associated with this disease. This review aims to support pediatricians with enough information to confidently diagnose pediatric PsO, assess associated physical and mental health comorbidities, and recommend first-line treatment options for children with mild to moderate PsO. To accomplish this, we provide information that distinguishes the appearance and symptoms of pediatric PsO from other common pediatric skin conditions. In addition, comorbidities and some of the mental health challenges associated with pediatric PsO are reviewed to help pediatricians provide appropriate care for patients in their clinical practice.

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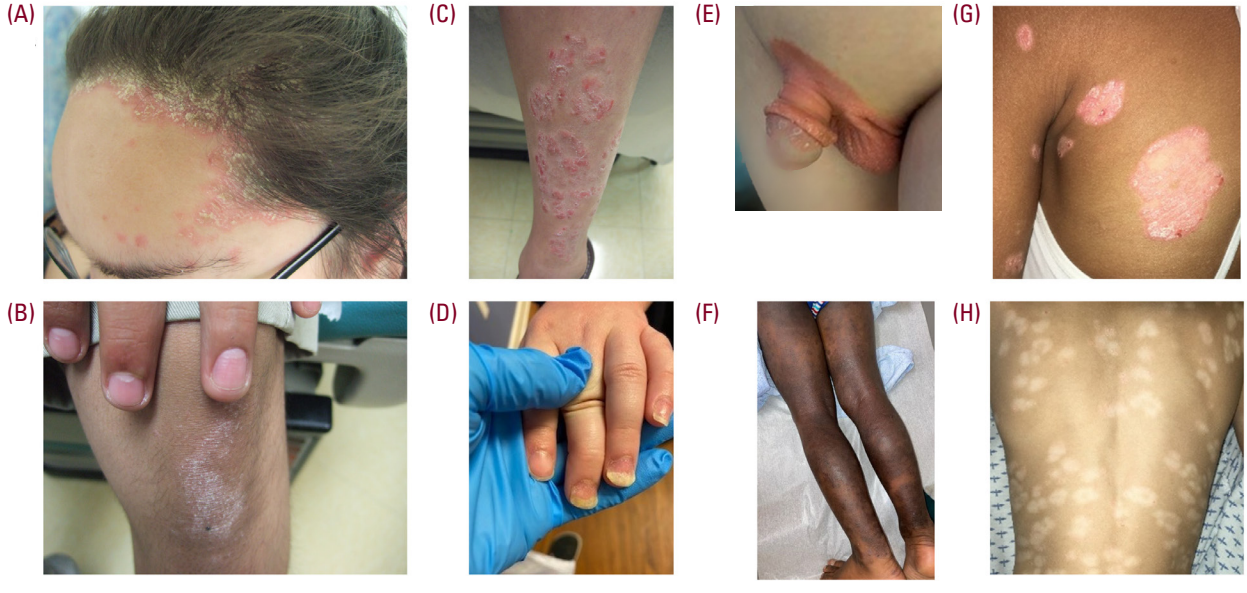
INTRODUCTION

Psoriasis (PsO) is a chronic, inflammatory skin disease characterized by cutaneous features, extracutaneous comorbidities, and an unpredictable course.[1,2] PsO is the second most common chronic pediatric skin disorder after atopic dermatitis (AD) and is reported to affect 0.05% to 2.15% of children,[3] compared with a 15% to 20% prevalence of eczema.[4] PsO is often mistaken for eczema because both are chronic diseases that feature red, scaly skin, suggesting that the true prevalence of pediatric PsO may be higher.[5] The mean age of onset of PsO is between 8 and 11 years, and the prevalence increases with age, estimated at 0.13% in those under the age of 2 years and 0.67% in teenagers.[6,7] Approximately 30% of adults with PsO experienced symptoms before the age of 20 years.[8]

Clinical features of PsO in infants and children are somewhat different from those of adults, which may also make distinguishing pediatric PsO from eczema more difficult. In an anonymous survey, 53.7% of pediatricians (n=95) reported being uncertain or very uncertain about their ability to diagnose pediatric PsO, despite regularly seeing pediatric patients with PsO.[1] Pediatricians who are less confident in their diagnostic ability are also less likely to perform total skin examinations, screen for relevant comorbidities, and prescribe disease-specific treatment. None of the pediatricians surveyed prescribed standard-of-care systemic immunomodulating agents (eg, methotrexate and/or cyclosporine) or US Food and Drug Administration (FDA)–approved therapies labeled for this condition (including targeted biologics or retinoids) for their patients with PsO. A French national survey of clinicians who treat children with PsO found a much lower use of severity scores and systemic treatments among general practitioners and pediatricians compared with dermatologists, thereby limiting treatment options for pediatric patients.[9] Dermatologists more frequently prescribed topical corticosteroids and vitamin D analogs for pediatric patients with PsO than general practitioners, suggesting a reluctance to prescribe or lack of awareness of preferred treatments for pediatric PsO.[10]

Early intervention in pediatric PsO can reduce the impact and burden of the disease and possibly its comorbidities, emphasizing the need for accurate and early diagnosis of pediatric PsO. This review describes the features and triggers that distinguish PsO

FIGURE 1. Common features of childhood-onset PsO include (A) scalp involvement, (B) scaling and (C) redness associated with plaques on the knees and lower legs, (D) nail pitting and onycholysis, (E) genital involvement, and hypopigmentation from plaques, as shown here in examples on the (F) legs, (G) underarm, and (H) back.



from eczema and other chronic inflammatory skin disorders in children; defines mild, moderate, and severe disease; highlights the challenges pediatricians face in the diagnosis and management of pediatric PsO; and discusses standard first-line treatment for mild to moderate pediatric PsO and emerging treatment options for moderate to severe disease.

Clinical Characteristics of Pediatric PsO

Evolving understanding of the complex characteristics of both pediatric PsO and eczema has allowed recognition of multiple subsets of both diseases, supporting the concept of these conditions as phenotypes rather than single diseases. The clinical hallmarks of pediatric PsO are sharply circumscribed, scaly plaques occurring in characteristic sites of predilection that define subtypes (Table 1 and Figure 1).[3,7,11-18] Large plaque PsO is the most common and well-recognized subset of PsO, reported in 69% to 75% of pediatric cases. These lesions typically involve the scalp, elbows, and knees.[7,11,12] Posterior auricular scale and nail pits are subtle findings that support the diagnosis.[19] Guttate (small plaque) PsO is the second most common subset, reported in 14% to 29% of pediatric cases.[20] An initial guttate presentation has been associated with greater PsO severity.[20] Streptococcal infection is a well-recognized trigger of guttate PsO,[21] which may clear after treating the infection with antibiotics. Tonsillectomy has been demonstrated to induce remission in a minority of children with guttate PsO.[22] Other sites of predilection include palms and soles (palmoplantar PsO), skinfolds (inverse PsO), and ear canals (psoriatic otitis externa), which can be isolated or seen in children with large or small plaque disease.

In pediatric patients with PsO, nail involvement occurs in 17% to 39% of cases, and scalp involvement occurs in 18% to 79% of cases.[20,23-26] Nail involvement occurs more frequently in boys, while scalp involvement is reported significantly more often in girls.[20] Nail involvement may be a sign of a more prolonged course; however, unlike adult PsO, nail involvement has not been directly linked to psoriatic arthritis (PsA).[27]

Less common PsO subtypes may be more difficult to recognize[16] and include PsO-eczema overlap, pustular, isolated palmoplantar, inverse, annular, petaloid, erythrodermic, and tinea amiantacea. Inverse PsO presents with well-demarcated, pink-to-red, often macerated plaques in the axillary, inguinal, and gluteal creases and the umbilicus[14,15] and can be confused with infectious or eczematous intertrigo.[14] Itching, irritation from sweating, and tenderness are common.

Infants with PsO often present with involvement of the face and diaper area; 26% of children with PsO have a history of diaper rash.[28,29] Plaques in this area are characteristically well demarcated and often feature marked erythema with minimal scale. Koebnerization, a diagnostic and therapeutic feature of PsO, is the tendency to develop skin lesions at sites of friction or minor skin trauma.[30] Thumb involvement, representing Koebnerization from thumb sucking, is also a common feature of PsO in infants.[31]

PsO Triggers

Factors such as infections, high body mass index, and

TABLE 1.

Clinical Spectrum of PsO[3,7,11-18]		
Subtype	**Signs/Appearance**	**Location**
Plaque		
Large plaque	• Most common subtype (69%-75% of pediatric cases) • Sharply circumscribed, erythematosquamous plaques	• Scalp, face, extensor surfaces of the elbow and knee, umbilicus, and buttocks - Scalp is frequently the first site of involvement
Small plaque (guttate)	• Second most common subtype (14%-29% of pediatric cases) • Small, round, raised plaques that are scaly with hyperkeratosis • Commonly triggered by streptococcal or viral infection - May clear after treating infection or develop into chronic PsO	• Trunk, abdomen, and back
Inverse	• Well-demarcated, pink-to-red, often macerated plaques • Itching, irritation from sweating, and tenderness are common	• Skinfolds - Axillary, inguinal, and gluteal creases and the umbilicus
Psoriatic otitis externa	• Similar to large plaque PsO	• Ear canals
Pustular		
Localized or generalized	• Less common than plaque PsO (1.0%-5.4% of pediatric cases) • Superficial sterile pustules • Often accompanied by fever	• Diffuse or localized to the fingers, palms, soles, toes, and nail beds
Annular	• Ring-shaped pustular lesions	• Can be diffuse or localized
Other		
Palmoplantar	• Plaque or pustular lesions • Scaly, red plaques or pustules with deep painful fissures	• Palms and soles
Linear	• Erythematous papules or plaques • Often accompanied by Koebnerization and Auspitz sign	• Distributed along the lines of Blaschko
PsO-eczema overlap	• Plaque or pustular lesions • PsO or eczema lesions can develop from their respective triggers	• Facial, scalp, and nail involvement
Nail	• Pitting, leukonychia, and subungual hyperkeratosis	• Nails
Paradoxical	• Develops in response to anti-TNF treatment for other skin conditions • Plaque or pustular lesions • Usually resolves after discontinuation of treatment	• Diffuse, but palmoplantar regions most often affected
Erythrodermic	• Erythema and scaling on >90% BSA • Can be accompanied by severe hypothermia and hypoalbuminemia • Extremely rare	• Diffuse

Abbreviations: BSA, body surface area; PsO, psoriasis; TNF, tumor necrosis factor.

cutaneous trauma can trigger pediatric PsO. Upper respiratory tract infection, particularly group A β-hemolytic streptococcal pharyngitis, and some drugs (eg, propranolol, antimalarials, terbinafine, and lithium as well as following withdrawal of systemic corticosteroids) are other well-recognized triggers.[11,32] Environmental exposure to tobacco smoke and stressful life events have also been associated with pediatric PsO.[33-35] Paradoxical PsO refers to an emerging subtype of PsO first recognized in adults but increasingly reported in children.[36-40] This subtype develops in patients treated with a biologic agent that blocks tumor necrosis factor (TNF). Agents that target this pathway are effective, FDA-approved medications for PsO but when used for other indications (inflammatory bowel disease [IBD] or arthritis) can trigger PsO.

Pathophysiology

Well-defined, but not mutually exclusive, inflammatory pathways distinguish plaque PsO from AD, as supported by the evolving pipeline of targeted biologic therapy. In vitro studies initially identified the helper T (TH) 1 pathway as the most important signaling pathway in the pathophysiology of PsO.[41,42] Early clinical trials that followed this discovery demonstrated that blocking TNF alpha led to significant improvement in PsO, but subsequent studies yielded even better improvements with agents that block interleukin (IL)-17 and IL-23.[43] In contrast, TH2 inflammation is the major immunologic pathway that impacts AD, as supported by successful treatment with biologic agents that block IL-4 and IL-13.[44]

Assessment of Pediatric PsO

A common assessment tool for determining PsO disease severity is total body surface area (BSA) involvement using the "rule of 9's" measurement, with adjustment of relative proportions of regions based on age.[32,45] The rule of 9's general guidelines are that the head and each arm comprise 9% of the total BSA, each leg and the front and back of the torso, respectively, each make

TABLE 2.

Features That Distinguish Pediatric PsO From Eczema[13,98-100]

	PsO	Eczema
Mean age of onset	8-11 years old	<2 years old
Clinical morphology		
Border	Sharp	Diffuse
Scale	Coarse	Fine
Pigment change	Hypopigmentation	Hyperpigmentation
Itch	+	+++
Sites of predilection	Face, scalp, axillary, inguinal and gluteal folds, umbilicus, palms/soles, diaper area, nail pits, orbital rim	Antecubital and popliteal fossae (spares diaper area)
Associated comorbidities	High BMI, hypertension, obesity, insulin resistance, metabolic syndrome, arthritis, IBD, PsA	Chronic rhinitis, asthma, food allergy, eosinophilic gastrointestinal disease
Triggers	Friction, minor skin trauma	Viral infection
Response to corticosteroids	Less effective, rebound after discontinuation, potential worsening	Very effective
Readily available biomarkers	-	High IgE, eosinophilia
Inflammatory pathways	TH1 and TH17	TH2
Cytokine targets	IFN-γ, IL-12, IL-17, IL-23, TNF-α	IL-4, IL-13, IL-25, IL-33

Abbreviations: BMI, body mass index; IBD, inflammatory bowel disease; IFN-γ, interferon gamma; IgE, immunoglobulin E; IL, interleukin; PsA, psoriatic arthritis; PsO, psoriasis; TH, helper T; TNF-α, tumor necrosis factor alpha.

up 18%, and the genitalia make up 1%. BSA involvement of <3% is considered mild, 3% to 10% is moderate, and >10% is severe disease. BSA is a component of the Psoriasis Area Severity Index (PASI), which also includes 4-point rating scales for erythema, induration, and flaking. Payers often require PASI scores before authorizing payment for newer, more expensive medications. However, PASI scores should not be the sole assessment of disease severity. Other important factors are involvement of sites that are difficult to treat topically (face, scalp, folds, groin, nails), arthritis, and psychometric symptoms such as social withdrawal.[32,45] The Children's Dermatology Life Quality Index (CDLQI) is a validated, easily usable tool for clinical experience and psychometric properties of PsO in pediatric patients age four years to 15 years and 11 months.[46] CDLQI may be used to evaluate pediatric patients' health-related quality of life (HRQOL) and considered along with PASI scores to determine the overall burden of disease in this age group. In fact, the Joint American Academy of Dermatology–National Psoriasis Foundation (AAD–NPF) guidelines recommend that both BSA and CDLQI be used as a measure of PsO severity.[45]

Differences Between Pediatric and Adult PsO

Children may be at higher risk for missed and/or delayed diagnosis compared with adults. The key clinical differences that distinguish childhood-onset PsO from that in adults include lesion morphology, sites of predilection, and disease burden. Plaques in children can be less indurated and the scale finer without the classic silvery quality.[7] Isolated involvement of the ear canals in children may be confused with otitis externa.[11] Eyelid margins are another site of predilection that can be isolated and mistaken for other forms of blepharitis.[19] Pruritus may often be present.

Differential Diagnosis of Pediatric PsO

Diagnosing pediatric PsO can be challenging for pediatricians, as the signs may appear similar to eczema, tinea, or other inflammatory skin conditions (Table 2). Pediatric PsO is not commonly associated with asthma or allergic rhinitis, whereas these are frequently found in patients with AD or members of their family. Both pediatric PsO and AD feature erythema, induration, and scale, and both respond to treatment with topical corticosteroids, but PsO is more likely to rebound with treatment discontinuation.[47] Eczema is often most prominent in the antecubital and popliteal fossae, flexor wrists, and dorsal aspects of the hands, while pediatric PsO lesions commonly localize to the scalp, palms, soles, and extensor surfaces of the elbows and knees.[47] Furthermore, eczema typically spares the diaper area and skinfolds, while PsO commonly involves this area. Nail involvement is another feature of pediatric PsO that can support differentiation from eczema,[47] although nail pits and dystrophy can occur in eczema, especially in the setting of paronychia. Misdiagnosis of pediatric PsO as eczema is also likely related to the higher frequency of eczema compared with PsO. Lesional skin biopsy can help distinguish pediatric PsO from other skin conditions.[11] Diagnostic histologic features include epidermal thickening with elongated rete ridges, hypergranulosis, and parakeratosis, but clinically atypical pediatric PsO is less likely to exhibit psoriatic histology. The histologic features of pediatric PsO have been reported in 57.6% of infants with this suspected diagnosis.[48] The inflammatory impact on pigmentation is

another feature that distinguishes pediatric PsO from eczema, with PsO most often causing hypopigmentation and eczema most often causing hyperpigmentation.[49] This feature is most apparent and upsetting for patients with darker skin tones. PsO-eczema overlap features skin signs of both eczema and PsO but may be less responsive to topical corticosteroids. Recognizing overlap is especially important when considering options for systemic treatment.[48]

Comorbidities

Extracutaneous comorbidities associated with pediatric PsO can contribute to the physical and psychosocial burden of disease and can negatively impact quality of life. Patients with pediatric PsO are at increased risk for arthritis, IBD, Crohn's disease, hypertension, bronchial asthma, hyperlipidemia, nail disorders, and arterial hypertension than those without pediatric PsO.[6,50,51] Obesity, diabetes, and metabolic syndrome have also been more frequently observed in pediatric patients with PsO than patients without PsO, suggesting that PsO is an independent risk factor for developing metabolic comorbidities.[51,52] PsO can also coexist with vitiligo, alopecia areata, and lichen planus, further complicating optimal treatment.[53] Hypermetabolic syndrome, in which elevated resting energy expenditure leads to insulin resistance and excessive breakdown of proteins and triglycerides, has also been associated with PsO.[54]

In light of these findings, the NPF and the Pediatric Dermatology Research Alliance (PeDRA) established the NPF-PeDRA–Pediatric PsO Comorbidity Screening Initiative, which recommends regular screenings for obesity, type 2 diabetes, dyslipidemia, hypertension, IBD, arthritis, mood disorders, and substance use disorder for pediatric patients with PsO.[55] These evidence-based guidelines are targeted toward all healthcare providers treating pediatric patients with PsO to help minimize the long-term health effects of PsO.

PsO-associated symptoms negatively impact psychosocial quality of life in children, resulting in a greater risk of mood disorders than are associated with healthy patients or those with other pediatric chronic diseases such as arthritis, asthma, and diabetes.[56-58] Pediatric patients with PsO reported a higher incidence of anxiety, depression, and suicidal ideation than pediatric patients without PsO.[50,59] Children aged 5 to 16 years with PsO or AD reported the greatest impairments in HRQOL compared with other common skin conditions such as localized eczema, acne, and urticaria.[60] These patients also reported greater impairments in HRQOL than children with epilepsy, enuresis, or diabetes.[60] Pediatric patients with PsO often experience teasing or bullying due to their appearance, which can negatively impact self-esteem and lead to feelings of social exclusion.[61] Of pediatric patients with PsO, 65% reported feeling stigmatization[62] due to bullying or teasing,[63] which negatively impacted family and social relationships.

Juvenile PsA is a chronic inflammatory disease affecting the joints that occurs in some patients with pediatric PsO and can complicate disease treatment and management strategies.[64] In an analysis using pooled US claims data, the estimated prevalence of PsA in pediatric patients with PsO was approximately 2%,[65] which is lower than the approximately 30% reported prevalence in adults.[66,67] However, since patients may present with signs of arthritis before or after development of pediatric PsO, the overall prevalence of arthritis in pediatric patients remains uncertain. In 80% of pediatric patients with juvenile PsA, joint inflammation develops before onset of skin disease, and the most common age ranges for joint involvement are 2 to 3 years and 10 and 12 years.[55] Juvenile PsA has been estimated to account for 6% to 8% of all cases of pediatric inflammatory arthritis.[68] Pediatric patients with PsA should be evaluated for uveitis.

Treatment Options for Pediatric PsO

Although an increasing number of treatments have been approved by the FDA for pediatric PsO, most treatments are prescribed off label. The currently available treatment options recommended by AAD–NPF guidelines are topical medications, phototherapy, oral retinoids, immunosuppressants, and biologic agents (Table 3).[69,70] A topical corticosteroid is most often used first line for children with mild to moderate PsO. A limited number of low-potency topical corticosteroids are the only choices labeled to treat pediatric PsO in children under the age of 12 years. Although narrowband UV-B phototherapy has been shown to be an effective treatment, second-line use in children is limited by cost and need for in-office visits 2 to 3 days per week. Coal tar can be used in combination with other therapies such as phototherapy. For patients with an inadequate response to topical treatments or with additional comorbidities, oral immunomodulating agents, such as methotrexate or cyclosporin, or systemic retinoids, such as isotretinoin or acitretin, may be used. Children with involvement that is widespread or affecting sites that are difficult to treat topically (such as the scalp, face, groin, palms, soles, and nails), juvenile PsA, or contraindication to oral agents are candidates for treatment with a biologic. Biologics that are labeled for pediatric use include inhibitors of TNF (etanercept in the United States and European Union and adalimumab in the European Union), IL-12/23 (ustekinumab), and IL-17A (ixekizumab and secukinumab). Dosing information and clinical trial results for biologics for the treatment of pediatric PsO were previously reviewed.[71] The topical phosphodiesterase-4 (PDE4) inhibitor roflumilast was also recently approved in the United States for the treatment of plaque PsO in patients ≥12 years. Other systemic medications currently under investigation for pediatric PsO include biologics such as the TNF inhibitor certolizumab pegol; the IL-17 receptor A inhibitor brodalumab; the IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab; oral PDE4 inhibitors such as apremilast; the tyrosine kinase 2 inhibitor deucravacitinib; and new nonsteroidal topicals such as tapinarof (an aryl receptor inhibitor).

TABLE 3.

Treatment Options for Pediatric PsO			
	Medication	**Mechanism of action**	**Adverse effects**
FDA-approved treatments			
Topical	Calcipotriene (available as a foam)[101]; approved for children aged ≥4 years	Synthetic vitamin D_3 analog	• Application site erythema • Application site pain
	Calcipotriene and betamethasone (available as ointment, suspension, and foam)[102]; approved for children aged >12 years	Combination synthetic vitamin D_3 analog and corticosteroid	In addition to the potential adverse effects from calcipotriene: • Erythema • Folliculitis • Pruritus • Vesiculation
	Roflumilast[103]; approved for children aged ≥12 years (including for intertriginous psoriasis)	PDE4 inhibitor	• Application site pain • Diarrhea • Headache • Insomnia • Upper respiratory tract infection • Urinary tract infection
Biologic	Etanercept[94]; approved for children aged ≥4 years	TNF inhibitor	• Infections • Injection site reactions
	Ustekinumab[104]; approved for children aged ≥6 years	IL-12/IL-23 inhibitor	• Nasopharyngitis • Upper respiratory tract infection • Headache • Fatigue
	Ixekizumab[97]; approved for children aged ≥6 years	IL-17A inhibitors	• Injection site reaction • Upper respiratory tract infection • Tinea infection
	Secukinumab[105]; approved for children aged ≥6 years		• Upper respiratory tract infection • Nasopharyngitis • Diarrhea
Off-label treatments			
Topical	Triamcinolone acetonide, budesonide clobetasol propionate, desonide, fluocinolone acetonide, fluocinonide, hydrocortisone, and triamcinolone[106]	Corticosteroids	• Skin atrophy • Telangiectasia • Striae distensae • Acne • Folliculitis • Purpura • May exacerbate dermatoses • Contact dermatitis • Cushing syndrome • Cataracts • Glaucoma • Symptomatic hypothalamic-pituitary-adrenal axis suppression
	Tacrolimus[107]	Calcineurin inhibitors	• Malignancy • Infections • Lymphomas • Skin malignancies • Skin burning or pruritus
	Pimecrolimus[108]		• Application site burning • Headache • Nasopharyngitis • Cough • Influenza • Pyrexia • Viral infection

TABLE 3. TABLE 3. (CONTINUED)

Treatment Options for Pediatric PsO			
	Medication	**Mechanism of action**	**Adverse effects**
Off-label treatments			
Topical	Tazarotene[109]	Retinoid	• Pruritus • Burning/stinging • Erythema • Worsening of PsO • Irritation • Skin pain • Photosensitivity
	Crisaborole	Nonsteroidal PDE4 inhibitor	• None observed
	Anthralin[106]	Blocks DNA synthesis and increases reactive oxygen species release	• Skin irritation • Staining of skin and nails
	Coal tar[106]	Not well understood; potentially through suppression of DNA synthesis	• Irritant contact dermatitis • Folliculitis • Photosensitivity to UV-A • Pediatric patients should use with caution
Nonbiologic systemic	Methotrexate[110]	Dihydrofolate reductase inhibitor	• Nausea • Anorexia • Stomatitis • Fatigue • Myelosuppression • Hepatotoxicity • Pulmonary fibrosis • Gastrointestinal irritation • Psychosis (rare)
	Cyclosporin[110]	Calcineurin inhibitor	• Nephrotoxicity • Hypertension • Impaired renal function • Cutaneous squamous cell carcinomas • Hypertrichosis
	Acitretin[110]	Systemic retinoid	• Teratogenicity • Birth defects • Hepatotoxicity • Cheilitis • Dryness of the eyes, nasal, and oral mucosa • Epistaxis • Xerosis • Brittle nails • Hair loss • Burning or sticky skin • Retinoid dermatitis • Photosensitivity
Phototherapy	Narrowband UV-B phototherapy[111]	Downregulation of immune cell activity	• Burning • Lesional blistering • Potentially carcinogenic • Erythema • Reactivation of herpes simplex • Varicella
Therapeutics that can potentially trigger or worsen PsO			
Biologics	Etanercept, infliximab, adalimumab, certolizumab pegol[18,36-40]	TNF inhibitors	• Can lead to aggravation of preexisting immune-mediated inflammatory diseases and trigger new inflammatory diseases, including psoriasis and Crohn's disease

Abbreviations: FDA, US Food and Drug Administration; IL, interleukin; PDE4, phosphodiesterase-4; PsO, psoriasis; TNF, tumor necrosis factor.

TABLE 4.

Indications for Referring a Child With Suspected PsO to a Dermatologist	
Clinical parameter	**Indicators**
Clinical signs	• Suspicion of PsO based on clinical signs and symptoms, especially based on location, severity, and duration of lesions - Presence of lesions in sites that are difficult to treat with topical medication such as genitals, scalp, nails, or palmoplantar areas - BSA >10% - Severity affecting quality of life
Response to treatment	• Lack of response to weak topical corticosteroid
Comorbidities	• Presence of comorbidities highly associated with PsO such as joint pain, diabetes, thyroid disease, and IBD
Other	• If diagnosis is not definitive

Abbreviations: BSA, body surface area; IBD, inflammatory bowel disease; PsO, psoriasis.

TABLE 5.

Pediatric PsO Resources for Patients and Their Families	
Resource	**Link**
National Psoriasis Foundation	https://www.psoriasis.org/
Over-the-Counter Topicals	https://www.psoriasis.org/over-the-counter/
Integrative Approaches to Care	https://www.psoriasis.org/integrative-approaches-to-care/
Media for Patients	https://www.psoriasis.org/watch-and-listen/
Patient Navigation Center	https://www.psoriasis.org/navigationcenter/
Our Spot for Youth and Parents	https://www.psoriasis.org/our-spot/
American Academy of Dermatology	https://www.aad.org/public
Psoriasis Resource Center	https://www.aad.org/public/diseases/psoriasis
Good Skin Knowledge Youth Education	https://www.aad.org/public/parents-kids/lesson-plans
Camp Discovery for Kids	https://www.aad.org/public/public-health/camp-discovery
Children's Skin Disease Foundation	https://www.csdf.org/
Camp Wonder	https://www.csdf.org/camp-wonder

Abbreviation: PsO, psoriasis.

Management of Pediatric PsO

Pediatricians can initiate first-line treatment for children with PsO beginning with a topical corticosteroid applied no more than once a day. In many cases, topical corticosteroid therapy will yield improvement but not clearing, and rebound worsening once treatment is stopped is common. A corticosteroid-sparing topical medication can be added to address either of these suboptimal responses. These medications include synthetic vitamin D analogs (calcipotriol and calcitriol) alone or as 2-ingredient combination vitamin D/corticosteroid products, as well as calcineurin inhibitors (tacrolimus and pimecrolimus), retinoids (tazarotene), coal tar, salicylic acid, and anthralin. A dermatologist is typically more familiar with second-line topical choices and indications for systemic treatment and can also provide access to phototherapy (Table 4).

Successful treatment requires shared medical decision-making so that patients and their families are comfortable with the treatment plan, including the relative risks and benefits of available options and long-term safety.[13,72,73] Dosing schedules or treatment reminders can support medication adherence.[74,75] In addition to treating skin signs and symptoms, successful management of pediatric PsO requires consideration of other aspects of the disease, including triggers and associated mental health issues.[7,13,45] Ideal long-term management depends on choosing a medication that will not worsen or optimally will improve coexisting medical conditions.[7] Children and adolescents with psychiatric comorbidities can benefit from counseling to help manage the negative mental components of the disease.[7,13]

For pediatric patients with PsO and their families, several informational, emotional, and social support resources are available (Table 5). The NPF provides useful information for how pediatric patients can manage their PsO, including diet and lifestyle changes, such as increased physical activity, that

can help reduce the risk of comorbidities.[76] Use of a moisturizer that contains scale softeners, salicylic acid, lactic acid, glycolic acid, urea, or the anti-itch ingredients pramoxine, menthol, or calamine can augment skin care.[77] Other alternative management approaches include acupuncture, apple cider vinegar for scalp itch, capsaicin added to topical medications, dilute bleach, Dead Sea or Epsom salt baths, or tea tree oil; however, these approaches lack clinical research on their long-term effectiveness and safety,[78] and some can sting or cause skin irritation. The NPF website provides articles, webinars, podcasts, and videos about PsO and PsA, including treatment options and management, news, and stories from patients with PsO.[79] Other support resources provided by the NPF include a free patient navigation center to help with questions about PsO and a peer support network that matches patients and caregivers with people who have experienced a similar situation and can provide guidance and reassurance.[80] "Our Spot for Youth" is a patient resource center that provides welcome kits for pediatric patients with PsO and their families, tips on communicating with teachers and friends, and downloadable school resources.[81] The AAD also provides a PsO resource center with information about the disease, diagnosis, and treatment options as well as skin, hair, and nail care guides for patients with PsO.[82] These resources include a youth education campaign, "Good Skin Knowledge," which provides lesson plans and handouts to teach kids about common skin, hair, and nail conditions, such as PsO.[83]

Children with skin conditions, including PsO, are eligible to attend specialty summer camps. This experience can help improve self-esteem, social skills, body image, and skin care routines.[84] The AAD Camp Discovery is a no-cost summer camp designed for pediatric patients with chronic skin conditions.[85] The Children's Skin Disease Foundation's Camp Wonder is a week-long summer camp opportunity for children with chronic and life-threatening skin diseases provided free of cost for campers.[86]

Current Challenges for Pediatricians in the Treatment of Pediatric PsO

Misdiagnosis can prompt treatment of PsO with an oral or parenteral corticosteroid. This approach is well known to trigger rebound worsening or even pustular flares. Other pediatric-specific challenges can complicate treatment, including tactile aversion to topical medications, needle phobia, and anticipatory nausea or emesis.[87] Among the many systemic options FDA approved to treat PsO in adults, only 5 drugs are currently approved by the FDA for moderate to severe pediatric PsO. Insurance coverage is often denied for off-label treatments.[88,89] When access is available, out-of-pocket treatment for PsO has been documented to cost an average of $2528 per year, an important factor that limits optimal treatment.[90] Due to the difficulty in diagnosing pediatric PsO, patients are often misdiagnosed and prescribed treatments that can worsen their disease (Table 3). As skin lesions often resemble a rash, patients with PsO who are treated at emergency clinics are often prescribed oral, topical, or systemic corticosteroids that can worsen their PsO. Patients with PsO who are misdiagnosed and treated with TNF inhibitors may experience induction or exacerbation of PsO. Pediatricians should be aware that prescribing corticosteroids before an accurate diagnosis is made is not best practice and should consult a dermatologist if there is uncertainty about a diagnosis.[88,89]

Pediatricians should also be aware of potential adverse effects when prescribing topical corticosteroids for children. Although these medications are a time-honored and cost-effective approach, long-term safety data are limited. Safety is supported by using the lowest potency product that is effective for the patient.[45] Higher potency topical corticosteroids used more than once a day and applied under occlusion (eg, diaper area) and on the face and fold carry the highest risk of skin barrier compromise, percutaneous absorption, and hypothalamic-pituitary-adrenal axis suppression.[45] Phototherapy can be time-consuming and require high out-of-pocket costs, and improvement is typically not appreciated for several weeks. Potential long-term adverse effects of phototherapy include photoaging, actinic keratoses, and skin cancer,[91] although this risk is lower for narrowband UV-B than combination UV-A plus topical psoralens.[92] The need for protective eyewear also poses special risks for children undergoing phototherapy, and isolated, underreported retinal burns have occurred in children unwilling to leave eyewear in place.[56]

PsO that requires long-term use of systemic medication carries risks of drug-specific, treatment-emergent adverse effects (Table 3). Injection site reactions are the most common adverse effect of biologic agents.[93] Long-term safety concerns with TNF inhibitors include increased risk of serious infections (eg, tuberculosis), development of autoimmune phenomena (ie, IBD, diabetes, and paradoxical PsO),[93] and lymphomas and other malignancies,[94] although there were no reported malignancies in a long-term safety study of etanercept treatment in pediatric patients with PsO.[95] Pediatric patients receiving secukinumab or ixekizumab should be monitored for new or worsening IBD, which has occurred in adult patients with PsO receiving these biologics.[96,97] However, no confirmed cases of treatment-emergent IBD in pediatric patients receiving secukinumab have been observed in clinical trials to date. Hypersensitivity reactions and serious infections have been reported for every biologic approved for use in children. There are no data on the impact of biologic agents on vaccine response; therefore, up-to-date immunization status is recommended prior to starting any of these medications. Avoiding live virus vaccines is recommended in all children receiving immunosuppressant or biologic medication.

CONCLUSION

Pediatrician familiarity with the clinical presentation, diagnosis, and treatment of pediatric PsO will allow earlier and more effective management, alleviation of the physical and psychosocial burdens, and referral for long-term treatment when indicated.

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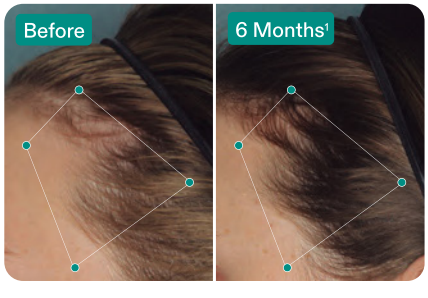

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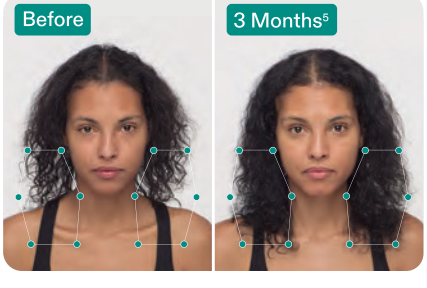

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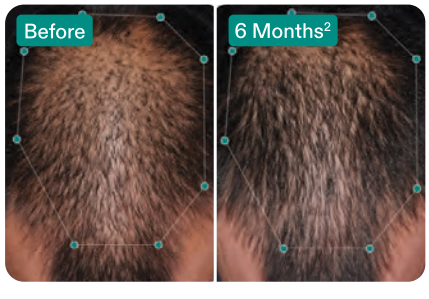

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Real-World Effectiveness and Safety of Tildrakizumab in Patients With Moderate-to-Severe Psoriasis: Week 28 Interim Analysis of a Phase 4 Study

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ABSTRACT

Background: Tildrakizumab is an anti–interleukin-23 p19 monoclonal antibody approved for the treatment of adults with moderate-to-severe plaque psoriasis. This analysis evaluated real-world effectiveness and safety of tildrakizumab for 28 weeks.

Methods: In this Phase 4 study (NCT03718299), adults with moderate-to-severe plaque psoriasis received tildrakizumab 100 mg subcutaneously at week 0, week 4, and every 12 weeks thereafter. Clinical improvement was assessed from Psoriasis Area and Severity Index (PASI) score change from baseline; disease activity from body surface area (BSA) percentage affected, static Physician's Global Assessment (sPGA), and sPGA x BSA; and safety from adverse events (AEs).

Results: At week 28, 52/55 enrolled patients were assessed. Mean (standard deviation [SD]) PASI score decreased significantly (P<0.001) from 11.6 (7.1) at baseline to 1.8 (3.0; 82.1% improvement) at week 28; 55.8% of patients achieved PASI 90 response. From baseline to week 28, mean (SD) BSA decreased significantly from 14.5% (11.5%) to 2.9% (6.4%), sPGA from 3.2 (0.6) to 1.2 (0.9), and BSA x sPGA from 47.0 (41.5) to 6.8 (20.3; all P<0.001). Serious AEs were infrequent. No treatment-emergent AEs were considered related to tildrakizumab.

Conclusions: Real-world tildrakizumab treatment significantly improved clinical status and reduced disease activity, with no new safety concerns.

J Drugs Dermatol. 2023;22(8):754-760. doi:10.36849/JDD.7471

INTRODUCTION

Plaque psoriasis is a chronic, inflammatory skin disorder spanning a patient's lifetime and hence requires long-term management.[1] Psoriasis is a multisystem disease that remarkably impacts patients' physical health and is associated with an increased incidence of comorbid conditions, including cardiovascular disease, Crohn's disease, type 2 diabetes, obesity, and lymphoma.[1-3] Psoriasis and its symptoms also have a considerable impact on patients' quality of life.[2]

Interleukin (IL)-23 is a key pro-inflammatory cytokine mediating psoriatic inflammation and tissue damage and is thus a target of plaque psoriasis therapy.[4,5] The p19 subunit of IL-23 is unique to this cytokine, while the p40 subunit is also present in IL-12.[4] Tildrakizumab, a high affinity, anti–IL-23 p19 monoclonal antibody, selectively binds to the p19 subunit, blocking its interaction with the IL-23 receptor. It is approved by the US Food and Drug Administration for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[6,7]

The efficacy and safety of tildrakizumab in patients with moderate-to-severe plaque psoriasis were assessed in 2 Phase 3, multinational, randomized clinical trials, reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754).[7-9] In the 64-week reSURFACE 1 trial, patients received a subcutaneous injection of tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo at baseline, week 4, and every 12 weeks thereafter. In the 52-week reSURFACE 2 trial, patients received a subcutaneous injection of tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo on the same schedule as in reSURFACE 1, with etanercept 50 mg (twice weekly to week 12, then weekly to week 28) as an active comparator. In both trials, at week 12, higher proportions of patients receiving tildrakizumab 100 mg achieved ≥75% and ≥90% improvement from baseline in Psoriasis Area and Severity Index (PASI) score (PASI 75 and PASI 90 response, respectively) and Physician Global Assessment (PGA) score of "clear" or "minimal" compared with patients receiving placebo.[7] Frequencies of adverse events (AEs) were favorable and similar among tildrakizumab treatment arms in

both trials.[7] Patients receiving tildrakizumab who successfully completed the reSURFACE 1 or reSURFACE 2 base study with at least a PASI 50 response were eligible to enroll in an optional extension study and receive the same dose of tildrakizumab for an additional 4 years. In pooled data analyses from reSURFACE 1 and reSURFACE 2, long-term treatment with tildrakizumab in patients who achieved a PASI 75 response at week 28 was associated with sustained disease control and a favorable safety profile for up to 5 years of total treatment.[9]

Although the efficacy and safety of tildrakizumab are well established in the clinical trial setting, little published real-world evidence is available from clinical practice settings. This manuscript reports the effectiveness of tildrakizumab in terms of clinical improvement and residual disease activity, as well as safety of tildrakizumab, from the week 28 interim analysis of a 64-week Phase 4 study in real-world practice.

MATERIALS AND METHODS

Study Design and Population

This Phase 4, open-label, real-world study was conducted at 2 sites in the United States, initiated in July 2019, and registered at www.ClinicalTrials.gov (record #NCT03718299). Eligible patients were immunocompetent, aged ≥18 years, had moderate-to-severe plaque psoriasis that was diagnosed at least 6 months prior to study entry, had ≥3% of their total body surface area (BSA) affected by psoriasis, and were candidates for phototherapy or systemic therapy. Patients were excluded from the study if they had erythrodermic psoriasis; only pustular, guttate, or inverse psoriasis; or evidence of skin conditions other than psoriasis that would interfere with study-related evaluations of psoriasis. Patients with prior or concomitant treatment with any biological agent other than tildrakizumab within 1 week prior to baseline, any new investigational drug within 12 weeks prior to baseline, or new treatment for psoriasis not used consistently prior to screening were also excluded. The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by a central Institutional Review Board, and all patients were required to provide written informed consent prior to study initiation.

Treatment and Assessments

All patients received tildrakizumab 100 mg by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter through week 52. The interim analysis was performed after all patients had the opportunity to complete treatment up to week 28. The investigator assessed patients' PASI scores at baseline and weeks 4, 16, and 28. The percentage of BSA affected and the static PGA (sPGA) were assessed by the investigator at baseline, every 4 weeks up to week 16, and at week 28. For the percentage of BSA affected, investigators could use the estimate that 1% BSA is equivalent to the area of the patient's closed hand. To determine sPGA, first, the psoriasis plaque attributes of induration, erythema, and scaling were rated on individual 6-point scales (0 = no evidence to 5 = severe), with each attribute averaged over the patient's entire body. Final sPGA was then obtained based on another 6-point scale (0 = clear, except for residual discoloration, to 5 = severe, lesions have individual induration, erythema, and scaling scores of at least 5).[10]

Safety was evaluated from AEs, which were reported spontaneously by patients or elicited by investigators during questioning and examination of a patient at any time during the study. AE data collected included date of onset, location (within/not within the affected region), severity (mild, moderate, severe), and relationship to treatment (not related, unlikely, possibly, probably, definitely).

Outcomes

The primary endpoint of the study, improvement in quality of life as measured by change from baseline in the total Psychological General Well-Being Index score, is reported elsewhere.[11] In this interim analysis, clinical improvement during tildrakizumab treatment through week 28 was evaluated from improvement from baseline in PASI score and the proportions of patients achieving 75%/90%/100% improvement from baseline PASI score (PASI 75/90/100 responses, respectively). Disease activity was evaluated from the percentage of BSA affected, sPGA, and sPGA x BSA over time.

Safety was assessed based on the incidence and severity of treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs through week 28.

Statistical Analysis

Sample Size

A sample size of 60 patients screened was selected to provide adequate estimates; no formal sample size calculations were performed. Following screening, 55 patients were enrolled in the study.

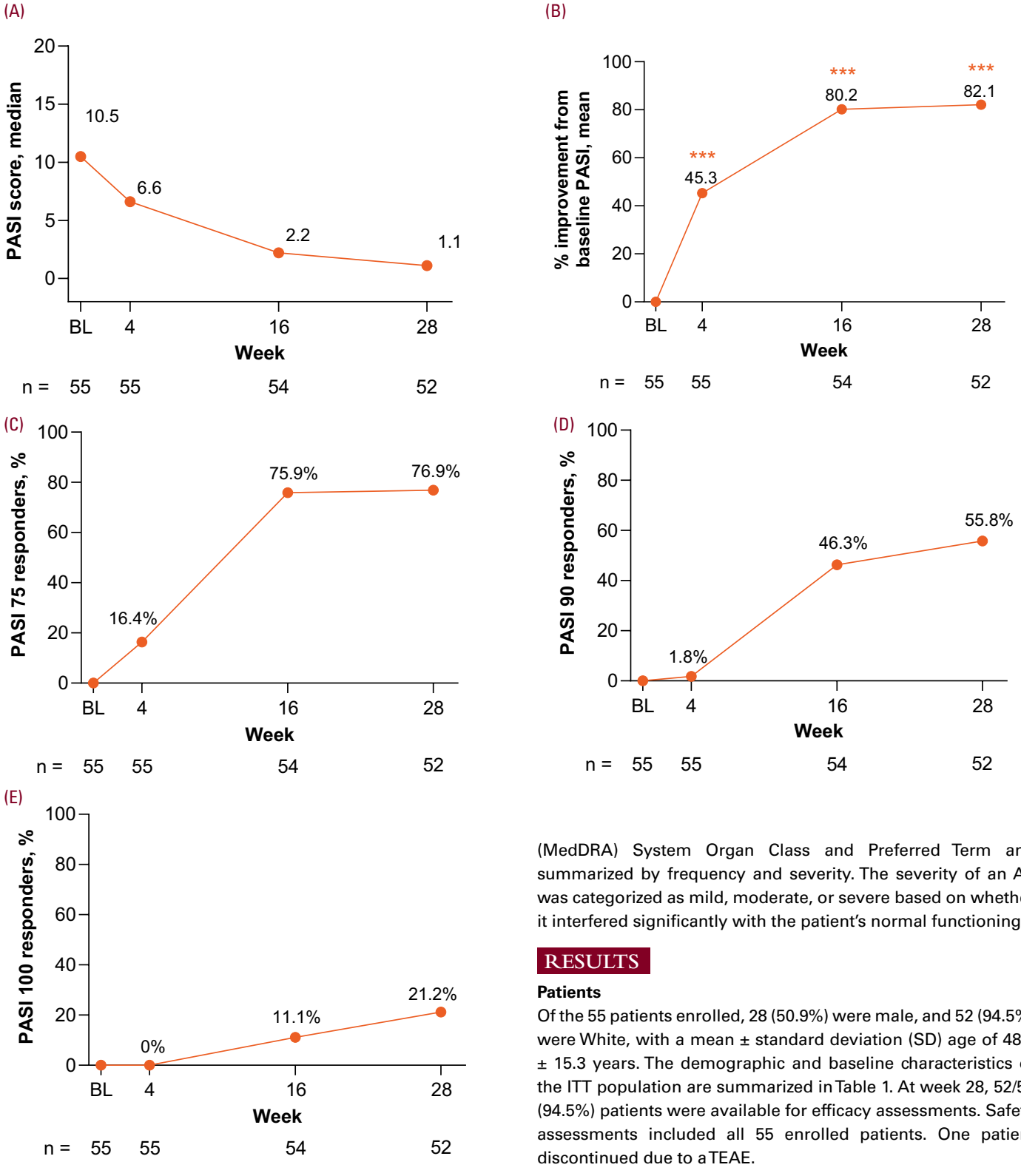
Effectiveness Analyses

Effectiveness was analyzed in the intention-to-treat (ITT) population, which consisted of all enrolled patients assigned to receive study medication. Descriptive statistics were calculated for the absolute values and percentage changes from baseline in PASI score, BSA, sPGA, and sPGA x BSA; the PASI 75/90/100 response rates were also summarized with descriptive statistics. Changes from baseline were analyzed using Student's t-test. Missing data were not imputed.

Safety Analyses

Safety analyses included all enrolled patients who received at least 1 dose of study treatment (safety population). The TEAEs were classified by Medical Dictionary for Regulatory Activities

FIGURE 1. Real-world treatment effectiveness through week 28 by PASI score. (A) Absolute PASI score, (B) Percentage improvement from baseline PASI score, (C) PASI 75 response rate, (D) PASI 90 response rate, and (E) PASI 100 response rate.



(MedDRA) System Organ Class and Preferred Term and summarized by frequency and severity. The severity of an AE was categorized as mild, moderate, or severe based on whether it interfered significantly with the patient's normal functioning.

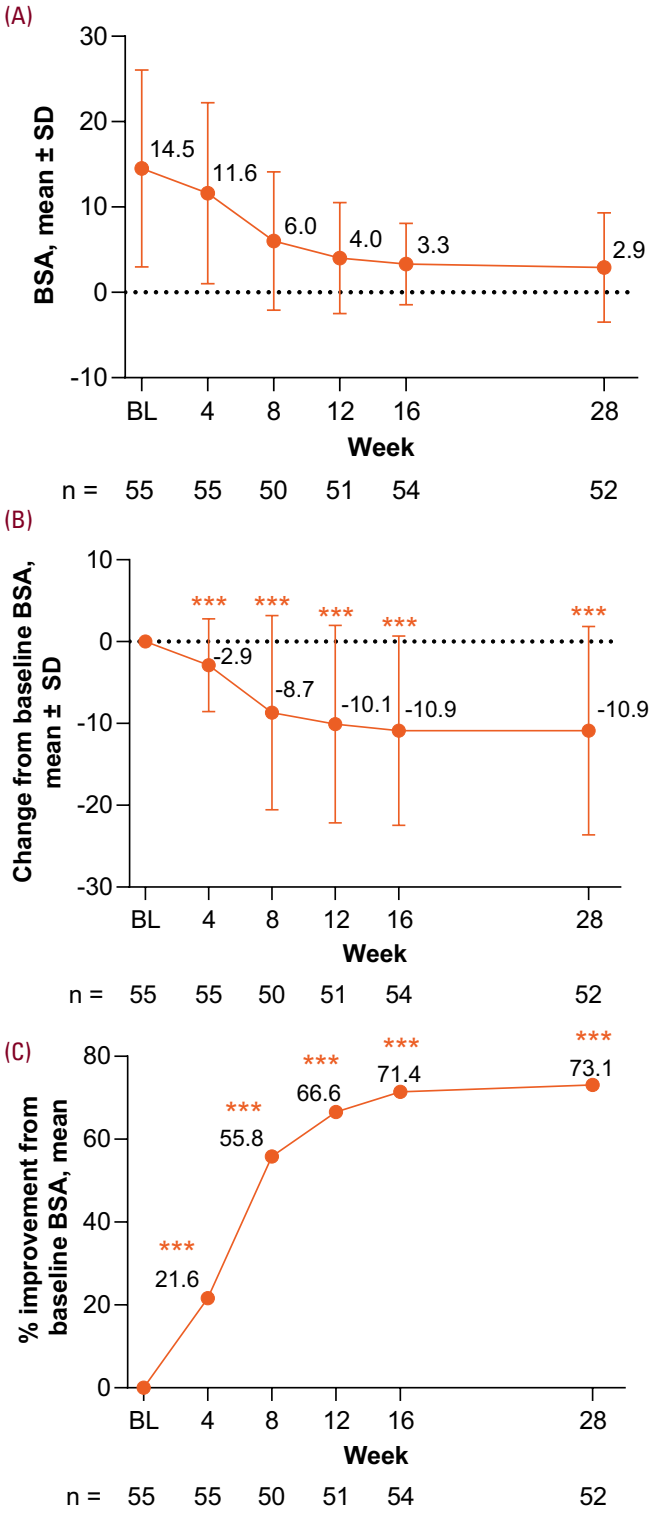
RESULTS

Patients

Of the 55 patients enrolled, 28 (50.9%) were male, and 52 (94.5%) were White, with a mean ± standard deviation (SD) age of 48.6 ± 15.3 years. The demographic and baseline characteristics of the ITT population are summarized in Table 1. At week 28, 52/55 (94.5%) patients were available for efficacy assessments. Safety assessments included all 55 enrolled patients. One patient discontinued due to a TEAE.

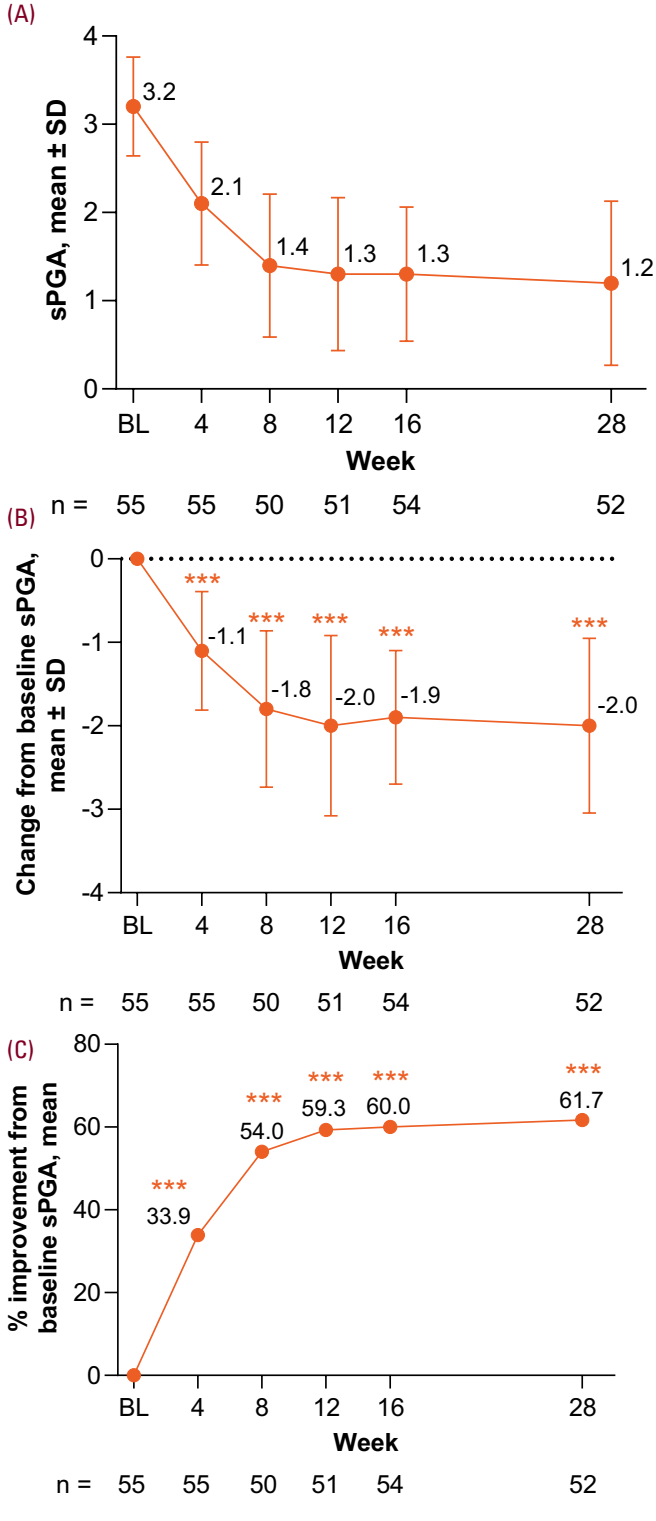
ITT population.
Data in panel A are shown as the mean; error bars represent the SD.
***P <0.001. n value reports number of patients assessed.
BL, baseline; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; PASI 75/90/100 response, 75%/90%/100% improvement from baseline PASI score; SD, standard deviation.

FIGURE 2. Real-world treatment effectiveness through week 28 by BSA. (A) BSA, (B) Absolute change from baseline in BSA, and (C) Percentage improvement from baseline BSA.



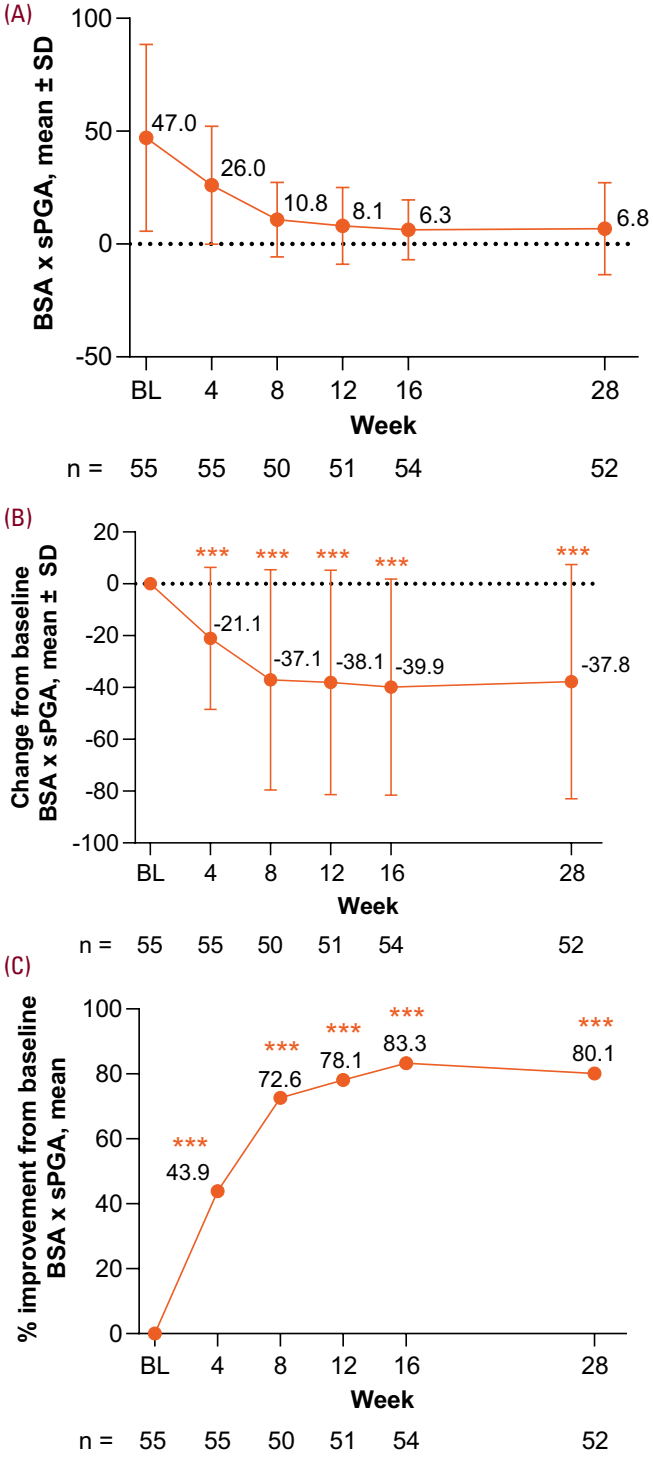
ITT population.
Data shown as the mean; error bars in panels A and B represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
***P<0.001. n value reports number of patients assessed.
BL, baseline; BSA, body surface area; ITT, intention-to-treat; SD, standard deviation.

FIGURE 3. Real-world treatment effectiveness through week 28 by sPGA. (A) sPGA, (B) Absolute change from baseline, and (C) Percentage improvement from baseline sPGA.



ITT population.
Data shown as the mean ± SD in panels A and B; error bars represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
***P <0.001. n value reports number of patients assessed.
BL, baseline; ITT, intention-to-treat; SD, standard deviation; sPGA, static Physician Global Assessment.

FIGURE 4. Real-world treatment effectiveness through week 28 by calculated BSA x sPGA. (A) BSA x sPGA, (B) Absolute change from baseline, and (C) Percentage improvement from baseline BSA x sPGA.



ITT population.
Data shown as the mean ± SD in panel A and B; error bars represent the SD.
Mean change from baseline at each visit in Panel B may not correspond to the difference between the mean at each visit and the mean at baseline in Panel A due to the different numbers of patients assessed at each visit.
*** $P<0.001$. n value reports number of patients assessed.
BL, baseline; BSA, body surface area; ITT, intention-to-treat; SD, standard deviation; sPGA, static Physician Global Assessment.

TABLE 1.

Demographics and Baseline Characteristics of the ITT Population	
	Tildrakizumab (N = 55)
Sex	
Male	28 (50.9)
Age, years, mean ± SD	48.6 ± 15.29
Race	
American Indian or Alaska Native	0 (0.0)
Asian	1 (1.8)
Black or African American	2 (3.6)
Native Hawaiian or Pacific Islander	0 (0.0)
White	52 (94.5)
Other	0 (0.0)
Not reported	0 (0.0)
Ethnicity	
Hispanic or Latino	5 (9.1)
Not Hispanic or Latino	50 (90.9)
Not reported	0 (0.0)
BSA, mean ± SD	14.5 ± 11.5
PASI, mean ± SD	11.6 ± 7.1
sPGA, mean ± SD	3.2 ± 0.6
BSA x sPGA, mean ± SD	47.0 ± 41.5

All data are n (%) unless otherwise noted.
BSA, body surface area; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

Effectiveness

Patients experienced significant improvement in disease severity by multiple measures as early as week 4, with further improvements by week 28. The PASI score decreased from a mean ± SD of 11.6 ± 7.1 (median, 10.5; range, 2.7 to 33.8) at baseline to 6.5 ± 5.1 at week 4 (mean percent improvement, 45.3%; $P<0.001$) and to 1.8 ± 3.0 at week 28 (mean percent improvement, 82.1%; $P<0.001$; Figure 1A–B). At week 28, the PASI 75 response rate was 76.9%, the PASI 90 response rate was 55.8%, and the PASI 100 response rate was 21.2% (Figure 1C–E).

Mean ± SD BSA decreased from 14.5 ± 11.5 at baseline to 11.6 ± 10.6 at week 4 (mean percent improvement, 21.6%) and further decreased to 2.9 ± 6.4 by week 28 (mean percent improvement, 73.1%; both $P<0.001$; Figure 2A–C). The mean ± SD sPGA was 3.2 ± 0.6 at baseline and decreased to 2.1 ± 0.7 by week 4 (mean percent improvement, 33.9%; $P<0.001$) and to 1.2 ± 0.9 by week 28 (mean percent improvement, 61.7%; $P<0.001$; Figure 3A–C). The mean (± SD) calculated sPGA x BSA decreased from 47.0 ± 41.5 at baseline to 26.0 ± 26.2 at week 4 (mean percent improvement, 43.9%; $P<0.001$) and to 6.8 ± 20.3 at week 28 (mean percent improvement, 80.1%; $P<0.001$; Figure 4A–C).

TABLE 2.

TEAEs Through Week 28	
Evaluation	**Tildrakizumab (N = 55)**
Any TEAE	31 (56.4)
Treatment-related TEAEs	0
Serious TEAEs	3 (5.5)
TEAEs leading to treatment discontinuation	1 (1.8)
Most frequent TEAEs (>3% of patients)	
Gastrointestinal disorders	6 (10.9)
Large intestine polyp	2 (3.6)
General disorders and administration site conditions	2 (3.6)
Infections and infestations	8 (14.5)
Nasopharyngitis	2 (3.6)
Upper respiratory tract infection	2 (3.6)
Metabolism and nutrition disorders	2 (3.6)
Musculoskeletal and connective tissue disorders	6 (10.9)
Arthralgia	2 (3.6)
Neoplasms*	3 (5.5)
Skin papilloma	2 (3.6)
Nervous system disorders	4 (7.3)
Skin and subcutaneous tissue disorders	11 (20.0)
Dermatitis	3 (5.5)
Eczema	2 (3.6)
Psoriasis	7 (12.7)
Vascular disorders	5 (9.1)
Hypertension	5 (9.1)

Data shown as n (%) of patients with event in the safety population reported according to MedDRA System Organ Class and preferred term.
*Includes benign, malignant, and unspecified (including cysts and polyps).
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Safety

Tildrakizumab treatment was generally well tolerated. TEAEs reported through week 28 are summarized in Table 2. TEAEs occurred in 31 (56.4%) patients; the most frequently reported were skin and subcutaneous tissue disorders (20.0%), infections and infestations (14.5%), musculoskeletal and connective tissue disorders (10.9%), and gastrointestinal disorders (10.9%). No TEAEs of tuberculosis, opportunistic infections, or inflammatory bowel disease occurred in this study. Serious TEAEs occurred in 3 (5.5%) patients (COVID-19 infection, cerebrovascular accident, immunoglobulin A nephropathy; n = 1 each). No TEAEs were considered related to tildrakizumab treatment. One AE of transitional cell carcinoma (1.8%) before week 28 led to discontinuation after week 28.

DISCUSSION

This week 28 interim analysis of data from a 64-week, Phase 4 trial provides insights into the effectiveness and safety of tildrakizumab treatment in community practice patients with moderate-to-severe plaque psoriasis. Significant clinical improvement from baseline was observed at week 28 based on PASI response thresholds, with low disease activity based on absolute PASI score, BSA, sPGA, and BSA x sPGA. No new safety concerns were identified.

Both clinical improvement and disease activity are important indicators of treatment effectiveness. Improvement is desirable to patients, especially those with a large disease burden at baseline; however, a patient with high baseline disease severity who experiences 90% improvement may still have clinically significant disease after treatment. Conversely, a patient with moderate disease severity at baseline may have very acceptable low disease severity after treatment despite not achieving response thresholds such as the PASI 90. The results of our study emphasize that real-world tildrakizumab treatment is effective in terms of both clinical improvement and disease activity.

There is a knowledge gap regarding the real-world effectiveness of biologic therapies for plaque psoriasis compared with the efficacy and safety observed in clinical trials. Randomized clinical trials enroll select patient populations with stringent inclusion and exclusion criteria. In contrast, real-world studies provide valuable insights from a patient-centric perspective and allow physicians and the greater medical community to see the effects of treatments from a far more generalizable context.[12] The results of this real-world analysis are consistent with those of the Phase 3 reSURFACE 1 and reSURFACE 2 clinical trials. In reSURFACE 1 and reSURFACE 2, 77% and 73%, respectively, of patients treated with tildrakizumab 100 mg for 28 weeks achieved PASI 75 response; 49% and 55%, respectively, achieved PASI 90 response.[7] The mean (SD) pooled PASI scores at baseline, week 12, and week 28 were 20.2 (7.7), 5.7 (7.0), and 4.6 (6.6), respectively. In addition, the overall frequencies of TEAEs were generally similar between the Phase 3 trials and the present study.[7]

AEs reported in the current analysis are consistent with the safety profile of tildrakizumab in clinical practice, with common TEAEs including nasopharyngitis and upper respiratory tract infection.[5]

LIMITATIONS

Limitations of this interim analysis include the lack of a comparator study arm, a relatively short duration of follow-up, and a limited number of patients

CONCLUSION

This interim analysis provides information on the effectiveness and safety of tildrakizumab treatment beyond clinical trials, demonstrating the impact of treatment on clinical outcomes in patients with moderate-to-severe plaque psoriasis in the real-world setting. The full 1-year results are expected to provide further insight into the safety and effectiveness of tildrakizumab in clinical practice.

Data Availability Statement: Data and other documents will be made available after publication, with no end date, to anyone who submits a reasonable request to the study sponsor.

DISCLOSURES

JH has been a speaker, advisor, and consultant for AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Boehringer Ingelheim, and Novartis; an advisor for Galderma, Mayne, and Sanofi Regeneron; an advisor and consultant for Ortho Dermatologic; and a speaker and advisor for Sun Pharma, Incyte, Leo Pharma, and Beiersdorf. JGV reports nothing to disclose. BS is an employee of Sun Pharmaceutical Industries, Inc. NB is an advisor, consultant, and investigator for AbbVie, Almirall, Arcutis, Beiersdorf, Biofrontera, Bristol Myers Squibb, Boehringer Ingelheim, Cara, Dermavant, Eli Lilly, EPI Health, Ferndale, Galderma, Genentech, InCyte, ISDIN, Johnson & Johnson, LaRoche-Posay, LEO Pharma, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and Verrica.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Review of Tapinarof: Novel Topical Treatment for Plaque Psoriasis in Adults

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ABSTRACT

Psoriasis is a chronic, immune-mediated, multisystem, inflammatory dermatological condition that is persistent and relapsing. Topical treatments are first line agents for mild to moderate plaque psoriasis. With proven efficacy and safety, topical corticosteroids are often used, although adverse effects and limitations for use exist. Tapinarof (Vtama®), a novel topical aryl hydrocarbon receptor modulating drug, was approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults in May 2022. A literature search of PubMed, MEDLINE, and ClinicalTrials.gov was conducted using the following keywords: tapinarof, psoriasis, GSK2894512. Articles published before January 2023 were included in this review. This review describes the preclinical and clinical studies demonstrating the efficacy and safety of tapinarof, its place in therapy, and relevance to patient care.

J Drugs Dermatol. 2023;22(8):761-765. doi:10.36849/JDD.7481

INTRODUCTION

Psoriasis is a chronic, immune-mediated, multisystem, inflammatory dermatological condition that is persistent and relapsing.[1] It affects 3.2% of the American adult population and an estimated 125 million people worldwide. The incidence is estimated to be 80 new cases per 100,000 person-years. The prevalence varies based on geographical region. For example, psoriasis prevalence is 0.5% in certain parts of Asia and as high as 8% in Norway.[2-4] The age of disease onset is usually before the age of 40 years. Two peak age ranges of disease onset exist. Most patients are affected between the ages of 18 to 39 years or 50 to 69 years. Various types of psoriasis exist including plaque, guttate, inverse, pustular, erythrodermic, nail, and psoriatic arthritis.[5]The clinical presentation of plaque psoriasis involves lesions characterized by sharp margins, erythema, and silvery scales. Psoriasis is associated with medical and psychiatric comorbidities such as autoimmune disease, cardiovascular disease, metabolic syndrome, lymphoma, melanoma, nonmelanoma skin cancer, and depression. The impact of the disease on occupational function and psychosocial morbidity has been described.[6] Severity of psoriasis can range from mild to severe disease.

Although there is no cure for the condition, several effective treatment options exist, and management strategies range from nonpharmacologic recommendations, topical drugs, phototherapy, and systemic agents, both biologic and non-biologic agents. Appropriate treatment of psoriasis involves recognition of the condition, patient-specific pharmacotherapy selection based on disease severity, monitoring of the treatment and disease progression, and treatment of comorbidities. Tapinarof (Vtama®), a topical aryl hydrocarbon receptor modulating drug was approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults in May 2022.[7] Tapinarof is the first and only non-steroidal topical drug option in its class for adults with plaque psoriasis.

MATERIALS AND METHODS

Data Selection

A search of PubMed, MEDLINE, and ClinicalTrials.gov databases was conducted for articles published before January 2023, to identify clinical and preclinical trials evaluating the pharmacokinetics, efficacy, or safety of tapinarof. The following search terms were used: tapinarof, psoriasis, GSK2894512. Relevant articles in English and results from human clinical trials were included. Additional articles were identified by hand from references. Data from the package insert was used to complement information found in cited references.

Chemistry and Pharmacology

Tapinarof (GSK2894512 or WBI-1001) is a non-steroidal, natural product. It is an isopropyl-substituted stilbene metabolite produced by gammaproteobacteria *Photorhabdus*.[8,9]

Structurally, tapinarof or 5-dihydroxy-4-isopropyl-trans-stilbene is a small molecular aryl hydrocarbon with a molecular weight of 254.32 g/mol.[7] In comparing its structure to other naturally produced stilbenes, it is a derivative of plant-derived polyphenol resveratrol.[9] Although similar in structure to resveratrol, the activity of tapinarof is significantly different.

The aryl hydrocarbon receptor (AHR) plays a role in the pathophysiology of psoriasis; abnormal AHR signaling is associated with skin barrier malfunction and inflammation.[10] Preclinical profiling studies demonstrate that tapinarof binds to AHR and induces expression of genes that downregulate the expression of inflammatory cytokines.[8] Additionally, tapinarof induces expression of genes involved in skin barrier formation and differentiation of keratinocytes via AHR signaling pathways.[8] Thus, keratinocyte differentiation and anti-inflammatory effects emerge as the major mechanisms for tapinarof in treating psoriasis.

Formulation and Preclinical Evaluation

Vtama® is formulated as a cream for topical use containing 10 mg of active agent tapinarof. The cream vehicle contains non-active ingredients that include benzoic acid, butylated hydroxytoluene, citric acid monohydrate, diethylene glycol monoethyl ether, edetate disodium, emulsifying wax, medium-chain triglycerides, polyoxyl 2 stearyl ether, polyoxyl 20 stearyl ether, polysorbate 80, propylene glycol, purified water, and sodium citrate dihydrate.[7]

Several pre-clinical studies have evaluated additional mechanisms of tapinarof and potential benefits for treating psoriasis. The phenol groups of tapinarof may scavenge reactive oxygen species (ROS) and induce expression of AHR pathways that express genes for antioxidant enzymes.[8] In animal studies, the anti-inflammatory effects of tapinarof played more of a role in psoriasis treatment than antioxidant activity.[8] Another study reported that tapinarof induces AHR-mediated secretion of interleukin-24 (IL-24) which may enhance its therapeutic effects.[8]

Phase 1 Studies

Four randomized, controlled phase I studies were conducted for topical tapinarof cream (1%) once daily (QD) versus vehicle in healthy adults.[11] A total of 376 participants were randomized across the 4 trials. Major objectives for each Phase I study were to evaluate cumulative irritation, contact sensitization, photo allergenicity, and phototoxicity, respectively.[11] Results from the cumulative irritation trial indicate that tapinarof cream (1%) QD had a slight potential for very mild irritation under exaggerated and repeated test conditions for 21 days.[11] Results from the other trials suggest that tapinarof cream (1%) is well-tolerated, non-sensitizing, non-phototoxic, and non-photoallergic.[11]

Phase 2 and 3 Studies

A Phase 2 and Phase 2b, randomized, double-blind, vehicle controlled, multicenter trial was conducted to evaluate the safety and efficacy of tapinarof 0.5% and 1% cream applied daily or twice daily in adult patients with plaque psoriasis. Adult patients ages 18 to 65 years who had a clinical diagnosis of chronic, stable plaque psoriasis for at least 6 months, body surface area (BSA) involvement 1% to 15% and a Physician Global Assessment (PGA) of psoriasis score > 2 were randomized to one of 6 treatment groups: 1% tapinarof twice daily; 1% tapinarof once daily; 0.5% tapinarof twice daily; 0.5% tapinarof once daily; vehicle twice daily; or vehicle once daily.

Patients were instructed to apply the cream to all lesions and to continue treatment of all original areas of involvement as well as new lesions. At 12 weeks, significantly more patients in the tapinarof groups attained a PGA score of clear or almost clear and a minimum 2-grade improvement in the static 5-point score from baseline as compared to the vehicle groups (65% [1% tapinarof twice daily], 56% [1% tapinarof daily], 46% [0.5% tapinarof twice daily], 36% [0.5% tapinarof daily], 11% [vehicle twice daily], 5% [vehicle once daily]; $P<0.05$). In addition, significant differences were reported in the percent of patients with > 75% improvement in the Psoriasis Area and Severity Index (PASI75) for patients in tapinarof groups as compared to the vehicle groups (65% [1% tapinarof twice daily], 56% [1% tapinarof daily], 46% [0.5% tapinarof twice daily], 46% [0.5% tapinarof daily], 16% [vehicle twice daily], 5% [vehicle once daily]; $P<0.05$).

When compared to the vehicle groups, percent of patients with > 90% improvement in the Psoriasis Area and Severity Index (PASI90), were significantly higher in the 1% tapinarof twice daily (39% vs 0%, $P=0.002$), tapinarof 1% daily (40% vs 0%, $P=0.001$) and the 0.5% twice daily group (31%, $P=0.008$). Clinical improvement was noted at two weeks of therapy and efficacy was maintained for four weeks after the end of study treatment. More patients in the tapinarof groups rated psoriasis symptoms as very or moderately improved at the end of 12 weeks ($P<0.05$).

Treatment-emergent adverse events (TEAEs) were reported in 45% - 65% of patients in the tapinarof groups [68% [1% tapinarof twice daily], 53% [1% tapinarof daily], 58% [0.5% tapinarof twice daily], 45% [0.5% tapinarof daily]), and 24 - 26% of patients in the vehicle groups (24% [vehicle twice daily], 26% [vehicle once daily]). The most common TEAEs were contact dermatitis and folliculitis. More patients in the tapinarof groups discontinued treatment due to TEAEs as compared to the vehicle groups (10% vs 1%). The authors concluded that tapinarof is efficacious and has an acceptable safety profile in adult patients with mild psoriasis.[12,13]

Another Phase 2a, multicenter, open-label study evaluated the safety and tolerability of tapinarof in 21 adults with extensive plague psoriasis (> 20% BSA involvement). At baseline, the majority of patients were white (76.2%), 61.9% had a PGA score of 3 (moderate disease) and 38.1% had a PGA score of 4 (severe). Patients were instructed to apply tapinarof 1% cream daily for 30 days, to all affected areas, including new lesions. Adherence was assessed via completion of a diary. All patients demonstrated improvement in PGA score by the end of the study period; 73.7%

had > 1-grade improvement and 31.6% experienced > 2-grade improvement. Improvements in mean PASI score (-59.56%) and mean % BSA change (-49.77%) were observed. TEAs were reported in 57.1% of patients, with folliculitis reported most commonly. None of the patients discontinued treatment due to adverse events. Tapinarof demonstrated efficacy over the 4 week treatment period and was well tolerated.[14]

Two identical randomized, multicenter, double-blind, vehicle controlled, phase 3 trials (PSOARING 1 and PSOARING 2) evaluated the efficacy and safety of tapinarof in patients with plaque psoriasis. Adults with stable, chronic plaque psoriasis and BSA involvement of 3 to 20% were treated with tapinarof 1% cream or vehicle control cream, administered once daily for 12 weeks. The use of biological agents and other systemic treatments such as apremilast, methotrexate, and glucocorticoids was prohibited for the duration of the trial and four weeks before baseline assessments. With the exception of non-medicated emollients, the use of topical treatments, including corticosteroids, was also prohibited for the duration of the trial and two weeks before baseline assessment.

At baseline, in PSOARING 1 and PSOARING 2 trials, 79.2% and 83.9% of patients had moderate disease, and mean body-surface area affected was 7.9% and 7.6%. The majority of the patients were white, had psoriasis for more than 10 years, and had moderate psoriasis. At 12 weeks, significantly more patients treated with tapinarof achieved the target PGA response, defined as a PGA score of 0 or 1 (PSOARING 1: 35.4% vs 6%, $P<0.001$; PSOARING 2: 40.2% vs 6.3%, $P<0.001$). Additional, significantly more patients treated with tapinarof achieved a PASI75 response (PSOARING 1: 36.1% vs 10.2%, $P<0.001$; PSOARING 2: 47.6% vs 6.9%, $P<0.001$). Statistically significant changes were noted in the mean change in the percentage of BSA affected by psoriasis in the tapinarof groups compared to vehicle cream groups (PSOARING 1: -3.5 vs -0.2%, $P<0.001$; PSOARING 2: -4.2% vs 0.1%, $P<0.001$). A PASI90 response was observed in more patients treated with tapinarof compared with placebo (PSOARING 1: 18.8% vs 1.6%, $P<0.001$; PSOARING 2: 20.9% vs 2.5%, $P<0.001$). There was no major difference noted in the number of patients who discontinued the trial (PSOARING 1: 20.9% for tapinarof vs 23.5% of vehicle cream %; PSOARING 2: 17.8% vs 17.4%). More patients in the tapinarof groups experienced an adverse event during the trial (PSOARING 1: 50.3% vs 22.4%; PSOARING 2: 54.5% vs 26.2%, $P<0.001$). The most reported adverse event was folliculitis, followed by contact dermatitis, and headache. The authors concluded that tapinarof is superior to the vehicle cream for patients with moderate plaque psoriasis and is well tolerated.[15]

PSOARING 3 trial is an open-label, multicenter continuation phase conducted to evaluate the safety of tapinarof 1% cream, applied daily for up to 40 additional weeks following completion of PSOARING 1 and 2 trials. Patients who completed 12 weeks of tapinarof or vehicle treatment in PSOARING 1 or 2, were eligible to enroll in PSOARING 3. Patients who achieved clearance of psoriasis (PGA score 0) in the first 12 weeks of the study, discontinued the study drug and were monitored for maintenance of remission. Tapinarof was restarted if the PGA score increased to > 2. Those with a PGA score of > 1, were instructed to apply tapinarof 1% cream daily to all affected areas, including new lesions. A total of 763 patients entered this study.

Similarly to PSOARING 1 and 2, the most common adverse effect was folliculitis (22.7%), followed by contact dermatitis (5.5%). Patients who received tapinarof in PSOARING 1 or 2, had lower PGA scores than those who received the vehicle. Overall, 40.9% of patients achieved psoriasis clearance at least once during the PSOARING 3 trial. The total duration of remittive therapy was approximately 4 months. The trial suggests that long-term therapy, for up to 52 weeks, with tapinarof offers continued improvement without an increase in adverse events.[16]

Safety

According to the PSOARING 1 and 2 studies, the most common adverse event reported by patients who received tapinarof was folliculitis in 23.5% of this group compared to 1.2% in the trial 1 vehicle group and 0.6% in the trial 2 vehicle group. One patient experienced a severe case of folliculitis in the tapinarof group in trial 1. Folliculitis led to trial discontinuation in 1.8% of tapinarof patients in trial 1 and 0.9% of patients in trial 2. Five percent of the patients receiving tapinarof developed contact dermatitis compared to 0.6% in the vehicle group in trial 1 with similar findings in trial 2. Headache was reported in 3.8% of tapinarof patients and 2.4% in the vehicle group in trial 1 with similar findings in trial 2. Reports of burning, stinging, or itching were low in both trials. There were no differences between tapinarof and vehicle groups with regard to laboratory values, vital signs, physical examinations, or electrocardiograms.[15] Similar to PSOARING 1 and 2, PSOARING 3 reported similar adverse events with the most frequent being folliculitis in 22.7% and contact dermatitis in 5.5%. Folliculitis and contact dermatitis did not worsen with long-term treatment according to PSOARING 3. A small percentage of patients discontinued tapinarof due to folliculitis (1.2%) or contact dermatitis (1.4%). The drug was well-tolerated as evidenced by the fact that more than 90% of patients had no irritation during all visits in the trial over the 40 weeks. Reports of burning, stinging, and itching were low in the majority of patients.[16]

Drug Interactions, Dosing, and Administration

There are no clinical studies examining the drug interactions of tapinarof topical cream. Tapinarof is not an inhibitor or inducer of cytochrome P450 enzymes.[7] Tapinarof 1% cream is intended for external use only. A thin layer of cream should be applied to the affected areas once daily. Unaffected areas of the skin should be avoided. It is recommended patients wash their hands following

application unless the intended treatment area is the hands. The cream should not be used on oral, ophthalmic, or vaginal areas.[7]

Place in Therapy and Relevance to Patient Care

Tapinarof (Vtama®) is indicated for the treatment of plaque psoriasis in patients aged 18 years and older. Tapinarof is not included in the Joint American Academy of Dermatology and National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with topical therapy as these guidelines were published in 2021 and the drug was approved in 2022.[17] First line treatment for mild to moderate plaque psoriasis commonly includes topical medications. Topical drugs can also be used as adjunctive therapies for patients who are receiving phototherapy or systemic treatments. With proven efficacy and safety, topical corticosteroids are the mainstay of topical psoriasis treatment. Tapinarof presents prescribers with a topical treatment option for patients who are unable to use corticosteroid drugs due to contraindications or adverse effects.

Topical corticosteroids cause local dermatologic adverse effects such as skin atrophy, folliculitis, telangiectasia, purpura, or striae. Patients who use topical corticosteroids on a chronic basis or apply these products to the face or intertriginous areas are especially susceptible to local skin adverse effects. Rebound flare-ups may occur with abrupt withdrawal of topical corticosteroids, especially with daily use of high-potency topical corticosteroids. Topical corticosteroids may worsen certain conditions such as acne, dermatitis, rosacea, and tinea infections. Although the risk is low, suppression of hypothalamic pituitary axis suppression, bone atrophy, and type 2 diabetes have been reported. The greatest risk for systemic adverse effects is associated with high-potency topical corticosteroids when used over large body surface area or under occlusion for more than four weeks. The concept of corticosteroid tapering to gradually reduce the frequency of use has been explored. Clinical guidelines mention strategies to minimize topical steroid adverse effects and tachyphylaxis such as switching to a lower potency corticosteroid, using corticosteroid intermittently, or combining treatment with a non-steroid medication.

Steroid-sparing drugs such as topical calcineurin inhibitors, vitamin D analogues, and retinoids may be used for maintenance treatment of plaque psoriasis. Topical calcineurin inhibitors are not FDA approved for the treatment of plaque psoriasis and the strength of recommendation for their use in clinical guidelines is weaker compared to topical corticosteroids. Vitamin D analogues are effective and safe in treating mild to moderate psoriasis and are available as prescription combination products with corticosteroids. Long-term use of Vitamin D analogues for mild to moderate psoriasis is supported by a Strength of Recommendation A and I-II Level of Evidence in the guidelines. Topical retinoid tazarotene is another non-steroid treatment option that is approved for mild to moderate plaque psoriasis. Tazarotene causes skin irritation and strategies to minimize irritation may necessitate short contact treatment, alternate day application, or switching to lower concentration formulations. Additionally, use of tazarotene in pregnant women is contraindicated and a negative pregnancy test is required two weeks before drug initiation.[17]

No head-to-head trials of tapinarof and other non-steroid topical psoriasis treatments are currently published. Tapinarof represents an additional non-steroid topical treatment for plaque psoriasis in adults that can be used to avoid corticosteroid-associated adverse effects, alternate with corticosteroids, or add as an adjunctive treatment to systemic medications. The remittive effect of the drug is evidenced by patient remission for four to six months after drug discontinuation. Unlike topical corticosteroids associated with multiple adverse effects, tapinarof has a favorable safety profile with the most noteworthy adverse effect in clinical trials being folliculitis. Although folliculitis occurred in nearly one-quarter of patients in clinical trials, it only led to trial discontinuation in less than 2% of subjects. The drug has been safely used long-term for up to an additional 40 weeks following the original 12 weeks of treatment in original clinical trials.[7] Unlike tazarotene, tapinarof is not associated with any negative pregnancy data. Tapinarof is an additional medication that is an option before initiating systemic treatments which are associated with more significant adverse effects. Patients whose psoriasis was not managed by other topical medications may benefit from use of tapinarof. One limitation of the drug is the cost which is approximately $1405 for a supply of 60 grams, without insurance coverage. The manufacturer offers a prescription savings card for eligible commercially insured patients.[18] Additionally, clinical trials investigating the use of tapinarof in pediatric patients with plaque psoriasis, children and adults with atopic dermatitis, and intertriginous plaque psoriasis are ongoing.[19-21]

CONCLUSION

Tapinarof (Vtama®) is a novel topical aryl hydrocarbon receptor modulating drug indicated for treatment of plaque psoriasis in adults. The drug represents an additional non-steroid topical drug in the treatment armamentarium for patients with plaque psoriasis. The efficacy of tapinarof in clearing psoriasis and its remittive effects are demonstrated in clinical trials. The favorable safety profile with the most common adverse effect being folliculitis translates into drug tolerability and adherence by patients. The characteristics of tapinarof described in this review demonstrate the drug is an appealing non-steroid treatment option for adult patients with plaque psoriasis.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

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Tildrakizumab in Combination With Topical Halcinonide 0.1% Ointment for Treating Moderate to Severe Plaque Psoriasis

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ABSTRACT

Background: This prospective, open-label study evaluated the effectiveness and safety of tildrakizumab plus topical halcinonide ointment in psoriasis patients.

Methods: Adults (age ≥18 years) with moderate to severe plaque psoriasis (body surface area [BSA] ≥10%, physician's global assessment [PGA] ≥3, psoriasis area severity index [PASI] ≥12) received tildrakizumab (100 mg; s.c.) at weeks 0, 4, and 16. Patients with BSA >3% at week 16 received additional halcinonide 0.1% twice daily for 4 weeks (week 20) and were followed for another 4 weeks (week 24); those with BSA ≤3% were followed to week 24.

Results: Twenty-five patients were enrolled (mean age 52.6 years; 68% male). The proportion of all patients achieving BSA ≤3% was 52.2% at week 16, 73.7% at week 20 (after 4 weeks of adjunctive halcinonide in patients with BSA >3% at week 16), and 84.2% at week 24 (4 weeks after halcinonide discontinuation). PASI 75 was attained in 60.9% of all patients at week 16, and 73.7% at weeks 20 and 24. In patients adding halcinonide, improvements from baseline in mean BSA, PGA, and PGA x BSA increased from week 16 (55%, 29%, and 64%, respectively) to week 20 (78%, 51%, and 88%, respectively), and were maintained through week 24. Quality of life improved with tildrakizumab monotherapy and further with adjunctive halcinonide. Adverse events (AEs) were infrequent. No serious AEs or discontinuations due to AEs were noted.

Conclusion: Tildrakizumab plus topical halcinonide ointment

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease prevalent in approximately 3% of adults in the United States.[1] It is characterized by marked inflammation and increased epidermal thickness resulting from infiltration of the skin with activated T cells and abnormal proliferation and differentiation of keratinocytes. Moderate to severe psoriasis is associated with a number of comorbidities including metabolic syndrome, cardiovascular and cerebrovascular diseases, depression, and anxiety.[2] Patients may also develop mental health conditions[2] and have reduced quality of life.[3]

No cure is currently available for psoriasis and treatments focus on controlling symptoms. Therapeutic options include topical therapy for limited psoriasis, and phototherapy, systemic medications, and biologic agents for extensive psoriasis.[4] For plaque psoriasis, the National Psoriasis Foundation suggests an acceptable treatment response of ≤3% affected body surface area (BSA) and a target response of BSA ≤1% after treatment for 3 months.[5]

Among biologic agents, tildrakizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to interleukin-23 (IL-23) and inhibits its receptor interaction.[6,7] Randomized controlled trials showed that tildrakizumab monotherapy was efficacious compared with placebo for psoriasis treatment and well tolerated in patients with chronic moderate to severe plaque psoriasis.[8-13]

For patients lacking an adequate response to biologics alone, combinations of biologic therapy with other psoriasis treatments can be used for improvement.[14-18] For example, topical medications have been shown to augment clinical responses without causing additional adverse effects when applied with biologics.[17,18] A phase 3b, randomized trial showed that significantly more patients with moderate to severe psoriasis attained an adequate response after treatment with etanercept plus topical clobetasol propionate foam vs etanercept monotherapy for 12 weeks.[19] Another randomized, controlled study found faster clearance of psoriasis lesions with a combination of adalimumab plus topical calcipotriol/betamethasone compared with adalimumab alone.[20] Safety outcomes were not affected by addition of topical medications in these studies.[19, 20]

In the present, real-world study, topical halcinonide 0.1% ointment – a highly potent corticosteroid for relieving inflammation and itching due to corticosteroid-responsive skin conditions[21] – was given as an adjunct therapy to patients

with moderate to severe plaque psoriasis who did not achieve an adequate response to tildrakizumab monotherapy. The effectiveness and safety of the combination therapy were evaluated.

MATERIALS AND METHODS

Study Design and Participants

This was a single center, prospective, open-label study to evaluate the effectiveness and safety of tildrakizumab (ILUMYA® [tildrakizumab-asmn], Sun Pharmaceutical Industries, Inc.) in combination with halcinonide ointment (HALOG® ointment [Halcinonide Ointment, USP] 0.1%, Sun Pharmaceutical Industries, Inc.) for treating moderate to severe plaque psoriasis. The study protocol was approved by an institutional review board and the study was conducted in accordance with ethical guidelines. Written informed consent was obtained by all patients before initiating treatment.

Adults (≥18 years) with chronic, moderate to severe, plaque-type psoriasis (BSA ≥10%, physician's global assessment [PGA] ≥3, and psoriasis area severity index [PASI] ≥12) who were candidates for phototherapy and/or systemic therapy were recruited. Exclusion criteria included active non-plaque forms of psoriasis; lab abnormality or medical conditions that could affect patient safety during the study; active or untreated latent tuberculosis; prior or concurrent malignancy; hepatitis B; recent treatment of psoriasis with ultraviolet (UV) B or psoralen plus ultraviolet-A radiation (PUVA) phototherapy, oral systemic medications, biologics, or topical therapies; recent use of antibiotics or any investigational drug; pregnancy or breastfeeding; and hypersensitivity to the excipients of study drugs. Patients who have received a live vaccine within 4 weeks prior to baseline or intend to receive a live vaccine during the study were also excluded.

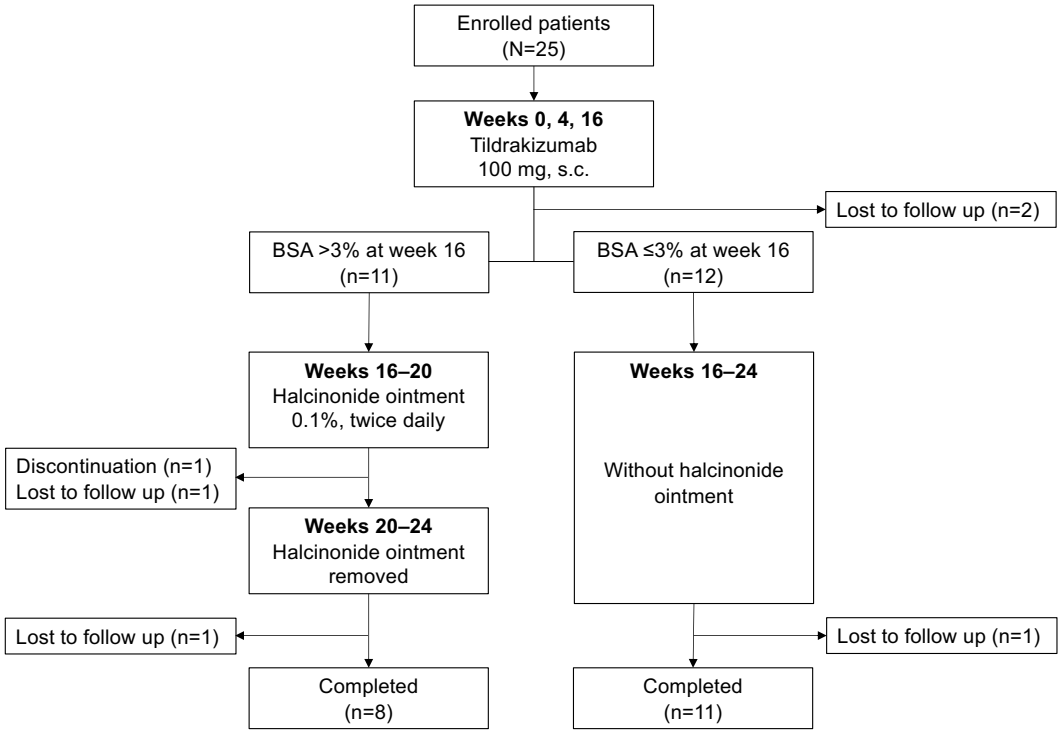
Study Treatment

All enrolled patients received tildrakizumab (100 mg) by subcutaneous injection at weeks 0, 4, and 16. Patients with body surface area (BSA) >3% at week 16 applied halcinonide ointment twice daily for 4 weeks and then continued without halcinonide for an additional 4 weeks of follow up. Patients with BSA ≤3% at week 16 were also followed up to week 24 (Figure 1). All patients were evaluated for safety and efficacy at weeks 4, 8, 16, 20, and 24 (Figure 1).

Study Outcomes

The primary endpoint of the study was the proportion of patients with BSA ≤3% at week 16. Secondary endpoints included proportions of patients with BSA ≤1%, dermatology life quality index (DLQI) of 0 or 1, and reduction of PASI score from baseline by 75%, 90%, and 100% (PASI 75, PASI 90, and PASI 100, respectively) at weeks 16, 20, and 24, in addition to proportions of patients with BSA ≤3% at weeks 20 and 24. Improvements in PGA, the composite PGA x BSA measure, and DLQI were also

FIGURE 1. Study design and patient disposition.



BSA, body surface area.

evaluated as secondary endpoints. Safety outcomes included adverse events (AEs) and serious AEs (SAEs).

Statistical Analysis

A cohort of approximately 25 participants was planned for enrollment in the study. Changes from baseline in BSA, PGA, PGA x BSA, PASI, and DLQI were summarized descriptively at weeks 4, 8, 16, 20, and 24; no formal statistical analyses were conducted given the sample size. AEs and SAEs were summarized descriptively by frequency and severity, and their causal relationship to treatment was assessed.

RESULTS

Patient Disposition and Demographics

A total of 25 patients were enrolled and 19 completed the study; 1 discontinued the study due to no response to treatment, and 5 were lost to follow up (Figure 1).

The majority of the patients were male (68%) and white (76%), with a mean age of 52.6 years (Table 1). Patients had psoriasis for an average of 18.9 years. Mean baseline BSA was 19.1%, and mean baseline scores were 3.5 for PGA, 16.7 for PASI, and 16.5 for DLQI (Table 1). At week 16, 12 patients had BSA ≤3%, while 11 had BSA >3% and received additional halcinonide ointment for 4 weeks (Figure 1).

Body Surface Area and Physician's Global Assessment Responses

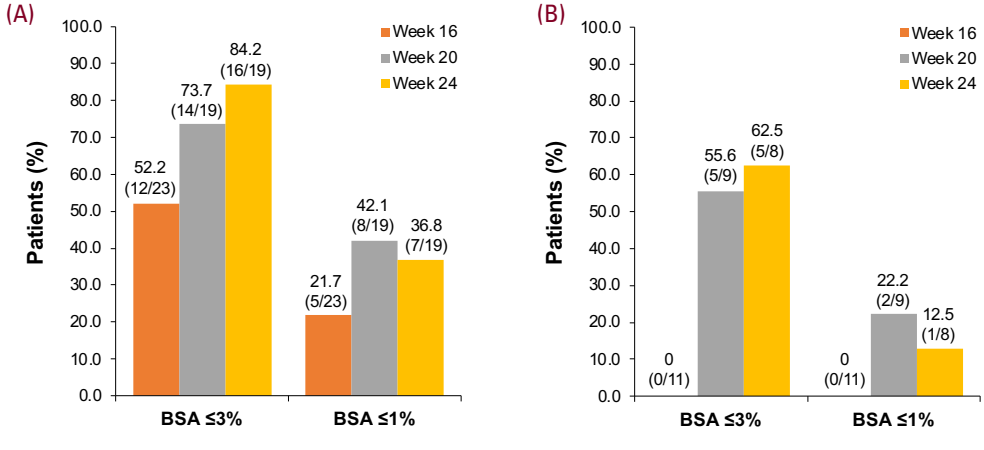
The proportion of all patients having affected BSA ≤3% with tildrakizumab was 52.2% at week 16. This percentage of all patients (both ≤3% and >3% BSA at week 16) increased to 73.7% at week 20 (after 4 weeks of additional halcinonide ointment applied in those with an unsatisfactory, week 16 response), and reached 84.2% at week 24 after patients had not been using halcinonide ointment for 4 weeks (Figure 2A). Of the patients who added halcinonide therapy at week 16, 4 achieved BSA ≤3% at week 20 and maintained the response level through week 24, 1 achieved BSA ≤3% at week 20 but lost the response at week 24 (BSA 6%), and 1 achieved BSA ≤3% at week 24; resulting in total 62.5% of this group achieving BSA ≤3% at study end (Figure 2B). Most patients who had BSA ≤3% at week 16 (no halcinonide use) and completed the study maintained a BSA ≤3% at weeks 20 and 24; the BSA of 1 patient increased to 4% at week 20, but dropped back to 3% at week 24. The proportion of all patients with BSA ≤1% also increased from 21.7% at week 16 to 42.1% at week 20, and was 36.8% at week 24 (Figure 2A). In patients who used halcinonide, 22.2% attained BSA ≤1% at week 20 and 12.5% at week 24 (Figure 2B).

Mean BSA involvement for all patients decreased from 19.1% at baseline to 5.0% at week 16 (74% reduction), 2.6% at week 20, and 2.7% at week 24 (86% reduction for both; Figure 3). Mean PGA and PGA x BSA of all patients also improved with treatment (Figures 4 and 5). In patients who had BSA >3% at week 16, the reduction from baseline in mean BSA, PGA, and PGA x BSA was 55%, 29%, and 64%, respectively, at week 16, and 78%, 51%, and 88%, respectively, at week 20 after 4 weeks of adjunctive halcinonide therapy; these responses were maintained at week 24 after halcinonide ointment had been stopped for 4 weeks (Figures 3-5). In patients who had BSA ≤3% at week 16 and did not use halcinonide, the mean scores of BSA, PGA, and PGA x BSA were reduced by 89%, 60%, and 95%, respectively, from baseline to week 16, and the responses were maintained through week 24 (Figures 3-5).

Psoriasis Area Severity Index Responses

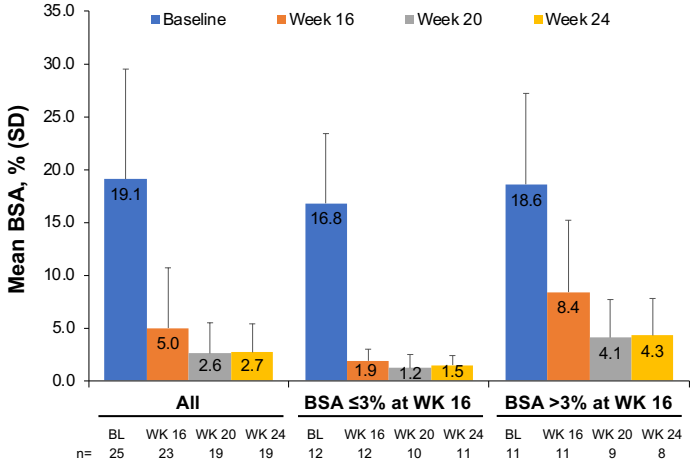
PASI 75 (≥75% reduction in PASI score vs baseline) was attained by 60.9% of all patients at week 16 in response to tildrakizumab monotherapy, and the percentage increased to 73.7% at weeks 20 and 24 (Figure 6).The proportion of all patients achieving PASI 90 also increased from 17.4% at week 16 to 52.6% at week 24 (Figure 6). PASI 100 (complete resolution) was achieved in 4.3%

FIGURE 2. Proportions of patients who achieved BSA ≤3% and BSA ≤1% at weeks 16, 20, and 24 (A) in all patients and (B) in patients with BSA >3% who received halcinonide at week 16.



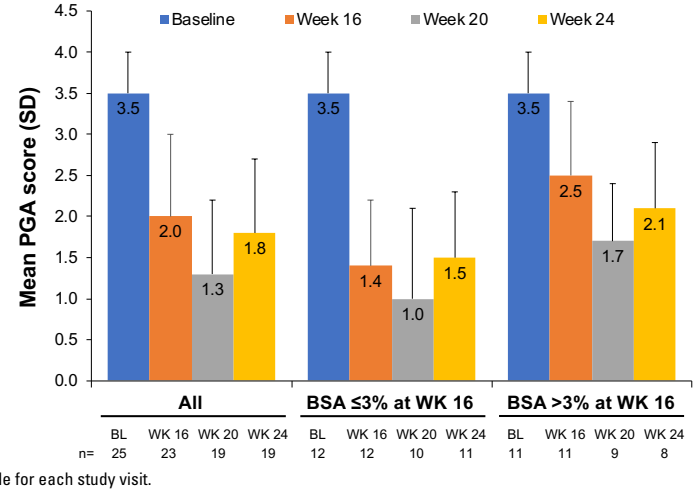
BSA, body surface area.

FIGURE 3. Mean BSA involvement at different time points for all patients, patients with BSA ≤3% at week 16, and patients with BSA >3% at week 16.



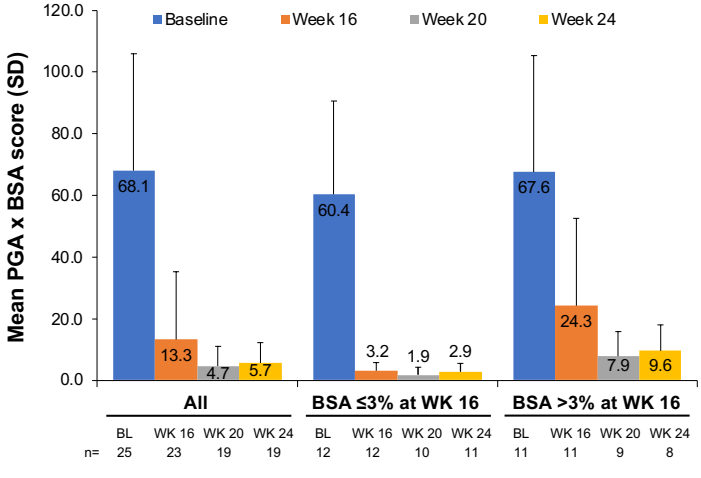
n indicates number of patients with data available for each study visit.
BSA, body surface area

FIGURE 4. Mean PGA score different time points for all patients, patients with BSA ≤3% at week 16, and patients with BSA >3% at week 16.



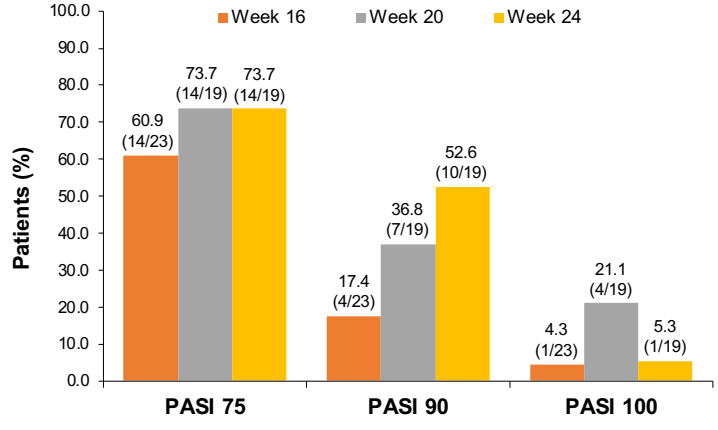
n indicates number of patients with data available for each study visit.
BSA, body surface area; PGA, physician's global assessment.

FIGURE 5. Mean PGA x BSA at different time points for all patients, patients with BSA ≤3% at week 16, and patients with BSA >3% at week 16.



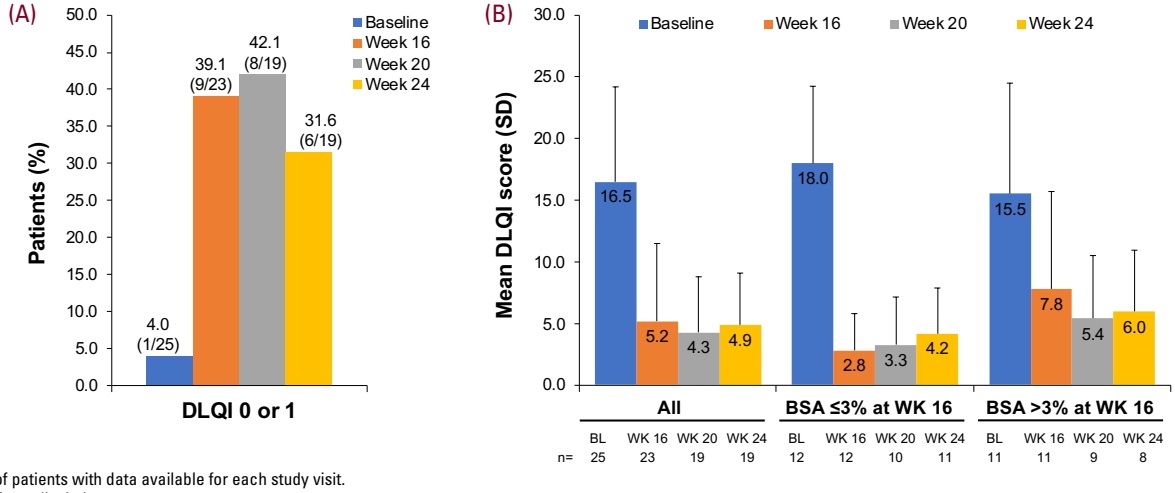
n indicates number of patients with data available for each study visit.
BSA, body surface area; PGA, physician's global assessment.

FIGURE 6. Proportions of patients achieving PASI 75, PASI 90, and PASI 100 responses in all patients at weeks 16, 20, and 24.



PASI, psoriasis area severity index.

FIGURE 7. Improvement in quality of life. (A) Proportions of patients achieving DLQI of 0 or 1, and (B) Mean DLQI at different time points for all patients, patients with BSA ≤3% at week 16, and patients with BSA >3% at week 16.



n indicates number of patients with data available for each study visit.
DLQI, dermatology life quality index.

of all patients at week 16 and 21.1% at week 20, although the percentage dropped to 5.3% 4 weeks after halcinonide therapy was stopped (Figure 6).

Quality of Life

With 16 weeks of tildrakizumab monotherapy, the proportion of all patients reporting a DLQI score of 0 or 1 increased from 4.0% at baseline to 39.2% at week 16, and continued to increase at week 20 (42.1%), but decreased to 31.6% at week 24 (Figure 7A). Mean DLQI of all patients decreased from baseline to week 16 by 68% and the improvement was maintained through week 24 (Figure 7B). In patients who had BSA >3% and used additional halcinonide ointment, the reduction in mean DLQI from baseline increased from 50% at week 16 to 65% at week 20 and 61% at week 24 (Figure 7B). In patients who had BSA ≤3% at week 16 and did not use halcinonide ointment, mean DLQI improved from baseline to week 16 by 84% and remained at similar levels at weeks 20 and 24 (Figure 7B).

Safety

A total of 10 AEs were reported in 8 (40%) patients during the study; 3 (rhinitis, cough, diarrhea) were considered treatment-related in 2 (8%) patients (Table 2). Most AEs (80% [8/10]) were mild, and the reported syncope and COVID-19 AEs were moderate in severity. No SAEs were reported and no patient withdrew from the study due to an AE.

DISCUSSION

In this real-world, prospective, open-label study, we showed that adjunctive use of topical halcinonide 0.1% ointment enhanced patient response to tildrakizumab. The proportion of all patients achieving BSA ≤3% and PASI 75 increased after just 4 weeks of additional halcinonide ointment applied to those who did not achieve an adequate response to tildrakizumab alone. All disease activity outcomes and patient quality of life improved with tildrakizumab monotherapy and further with the addition of halcinonide ointment. Importantly, the improvements were

TABLE 1.

Demographic and Baseline Characteristics	
Characteristic	**N=25**
Age, years	
Mean ± SD	52.6 ± 13.4
Range	25–83
Gender, n (%)	
Male	17 (68.0)
Female	8 (32.0)
Race, n (%)	
White	19 (76.0)
Asian	3 (12.0)
Black	2 (8.0)
Native American	1 (4.0)
Ethnicity, n (%)	
Non-Hispanic/Latino	16 (64.0)
Hispanic	9 (36.0)
Years of psoriasis	
Mean ± SD	18.9 ± 16.2
Range	1–56
Baseline BSA, %	
Mean ± SD	19.1 ± 10.4
Range	10.0–55.0
Baseline PGA	
Mean ± SD	3.5 ± 0.5
Range	3.0–4.0
Baseline PASI	
Mean ± SD	16.7 ± 4.6
Range	12.0–31.6
Baseline DLQI	
Mean ± SD	16.5 ± 7.7
Range	1.0–29.0

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, psoriasis area severity index; PGA, physician global assessment.

TABLE 2.

Demographic and Baseline Characteristics	
	n (%)
Number of any AEs	10
Number of treatment-related AEs	3
Patients with ≥1 any AE	8 (32)
Patients with ≥1 treatment-related AE	2 (8)
Patients with any SAE	0
Discontinuation due to any AE	0
List of AEs	
Candidiasis	1 (4)
Cough	1 (4)
COVID-19	1 (4)
Diarrhea	1 (4)
Pruritis	1 (4)
Psoriatic arthritis	1 (4)
Rhinitis	1 (4)
Rosacea	1 (4)
Syncope	1 (4)
Worsening of depression	1 (4)

AE, adverse event; SAE, serious adverse event.

maintained 4 weeks after halcinonide ointment was stopped. In addition, tildrakizumab alone or in combination with halcinonide ointment was well tolerated and no SAEs were noted in the study.

Our study reinforces the results from previous studies showing that tildrakizumab effectively controlled moderate to severe plaque psoriasis. In a randomized, controlled, phase 2b study, 64% of patients achieved PASI 75 and 52% had DLQI of 0 or 1 after 16 weeks of treatment with 100 mg tildrakizumab.[9] The randomized, controlled, phase 3 reSURFACE 1 and reSURFACE 2 studies further confirmed the efficacy of tildrakizumab, showing that approximately 70% of patients attained PASI 75 response at weeks 16 to 28 and approximately 40% of patients had a DLQI of 0 or 1 at week 12 with 100 mg tildrakizumab. Our study found a response rate of 60.9% for PASI 75 and 39.1% of patients who had a DLQI score of 0 or 1 at week 16 with tildrakizumab monotherapy, consistent with previous studies. In addition, the BSA ≤3% response level was generally maintained through week 24 with tildrakizumab alone in patients who attained it at week 16, in agreement with previous reports of the efficacy of tildrakizumab being maintained through week 28.[9,10]

In our cohort, almost half of patients did not achieve BSA 3% with tildrakizumab monotherapy at week 16 and were therefore in need of adding adjunctive therapies or switching to a new one. We found that 4 weeks of adjunctive use of topical halcinonide ointment effectively improved all outcomes in these patients, reflected in the decreased mean BSA, PGA, and BSA x PGA and the increased proportion of all patients with BSA ≤3% from week 16 to week 20. Moreover, the enhanced responses were maintained through week 24 after the additional halcinonide ointment had been stopped for 4 weeks. To our knowledge, this is the first report on a combination therapy of tildrakizumab with a topical medication. We showed that patient response to tildrakizumab could be augmented with the addition of halcinonide ointment, without the need to increase tildrakizumab doses or switch to a new biologic agent.

We found the tildrakizumab and halcinonide ointment to be safe and tolerable as most of the AEs were mild and not

treatment-related, and no SAEs or discontinuation due to AEs were reported in our study. This agrees with previous studies showing that 100 mg tildrakizumab was well tolerated for up to 3 years and frequencies of treatment-related AEs, SAEs, and discontinuations due to AEs with tildrakizumab were lower or comparable vs placebo.[9-13] These studies also showed that nasopharyngitis was the most common treatment-emergent AE in patients on tildrakizumab, with cough, diarrhea, and pruritus being commonly reported as well.[9-13] The 3 treatment-related AEs (rhinitis, cough, and diarrhea; 1 event each) reported in our study were therefore not unexpected with tildrakizumab. Topical corticosteroids are generally safe with infrequent local adverse reactions;[21] and the combination of tildrakizumab with halcinonide ointment did not appear to cause any additional safety signals in the present study.

Our study has a few limitations with its open-label design and a relatively small patient population. The study also lacked control arms. However, such limitations are typical for studies investigating the usefulness of treatment in a real-world setting. Moreover, our results were consistent with previous findings from larger randomized controlled trials, and clear improvements in psoriasis control among patients without an adequate response to tildrakizumab alone were observed. Study of the combination therapy for a longer duration beyond 24 weeks is warranted to investigate its longer-term effectiveness and safety.

CONCLUSION

This study demonstrated that patients with moderate to severe plaque psoriasis who inadequately responded to tildrakizumab monotherapy improved with adjunctive use of topical halcinonide 0.1% ointment. Improvements in BSA involvement, PGA, PGA x BSA, and DLQI were observed after just 4 weeks of halcinonide ointment being added to tildrakizumab, and were well maintained following discontinuation of the topical therapy. The combination was safe and well tolerated. Overall, our results support that the addition of topical halcinonide 0.1% ointment to tildrakizumab is an effective and safe treatment option to improve psoriasis control.

DISCLOSURES

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ORIGINAL ARTICLE

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Psoriasis and Skin Barrier Dysfunction: The Role of Gentle Cleansers and Moisturizers in Treating Psoriasis

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ABSTRACT

Background: Psoriasis is a chronic immune-mediated dermatologic disorder with multisystemic comorbidities, which is effectively treated with a range of prescription therapies. Studies have reported epidermal barrier abnormalities in the lesional skin of psoriasis patients; however, there is currently insufficient information about skin barrier function in psoriasis patients. This review discusses the potential role of gentle cleansers and moisturizers in the management of psoriasis and in promoting a healthy skin barrier.

Methods: A literature review was followed by the authors' discussions and agreement on 5 statements to provide expert guidance for gentle cleansers and moisturizer use in psoriasis patients.

Results: In a workshop, the authors provided feedback on 15 draft statements created prior to the meeting, and agreed upon 5 statements. The authors agreed that guidelines rarely mention skincare for psoriasis patients, demonstrating a potential knowledge gap. Skincare may play a role in managing psoriasis as an adjuvant treatment of acute psoriasis and for maintenance treatment of healing skin during asymptomatic periods. Studies of patients with psoriasis applying topical moisturizers (such as those containing salicylic acid or ceramides) showed softened plaques, enhancing the absorption of topical treatments such as corticosteroids. Studies applying ceramide-containing skincare showed an overall improvement in the appearance of the skin and provided relief for psoriasis.

Conclusion: The authors agreed that skincare and barrier restoration in treating psoriasis is a relatively new concept for most dermatologists. There is a need to develop a more robust body of evidence on skincare for psoriasis to influence clinical practice in a meaningful way.

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INTRODUCTION

Psoriasis is a chronic, immune-mediated, multisystemic skin disease with an estimated prevalence rate of over 2% of the United States population.[1] Adults are more frequently affected by psoriasis than children, and generally, there are 2 peaks of onset, the first at 16 to 22 years and the second at 50 to 60 years.[2,3] About 70% to 80% of psoriasis patients suffer from a mild-to-moderate disease that can be successfully controlled with topical treatments.[4] Moderate-to-severe cases are usually treated with ultraviolet (UV), oral, or biological therapies.[4] Concomitant topical treatments and skincare can support the efficacy of systemic treatments.[5]

Psoriasis significantly negatively impacts a patient's health-related quality of life (HRQoL).[6,7] Psoriasis patients often experience difficulties with body image, self-esteem, and feelings of stigma, shame, and embarrassment regarding their appearance.[6,7] Patients have reported the perception of being evaluated by others based on their skin condition.[6,7] Psoriasis causes a more significant reduction in quality of life (QoL) than tumors or coronary heart disease.[6,7] The median disease duration is about 50 years, especially when the onset is at a young age. Patients with psoriasis have significantly fewer employment opportunities.[7] Effective short- and long-term management of psoriasis is crucial to ensure sufficient control

of the disease and limit the burden of the disease and its impact on QoL and the ability to work.[7]

The multifactorial pathophysiology of psoriasis involves genetic, environmental, and immunologic factors.[8,9] Psoriatic lesions are characterized by inflammation, epidermal hyperproliferation, abnormal keratinocyte differentiation, and skin barrier dysfunction.[8-10] Inflammatory skin diseases are often associated with skin barrier dysfunction; although the cause-and-effect relationship is complex.[9] Psoriasis and gene mutations within the epidermal differentiation complex are associated with development, maturation, cornification, cross-linking, and thermal differentiation.[9-12] Alterations to several structures in the epidermal barrier in psoriasis might be responsible for barrier dysfunction leading to hyperproliferation of the epidermis.[9,10]

Skincare is rarely mentioned in published guidelines and algorithms to treat psoriasis, unlike atopic dermatitis.[13-15] There is a knowledge gap concerning using moisturizers, either alone or as adjunctive therapy, to restore skin barrier function, reduce symptoms, and delay relapse in patients with psoriasis.[15] This review aims to summarize aspects of skin barrier dysfunction in patients with psoriasis and to provide insights into the role of gentle cleansers and moisturizers in managing psoriasis and promoting a healthy skin barrier and better patient outcomes

MATERIALS AND METHODS

On July 21, 2022, an expert panel composed of 6 dermatologists (5 American and 1 Canadian) who commonly manage psoriasis patients was convened in Vancouver, British Columbia, Canada. The panel used the Delphi communication technique for interactive decision-making for medical projects for the review.[12,13] In preparation for the meeting, a literature review was conducted on skin barrier dysfunction in psoriasis, possible implications for the management, and the potential role of skin care.

Literature Review

A structured search of the English-language literature on skin barrier dysfunction and skincare in psoriasis was performed on June 17, 2022, using PubMed, with Google Scholar as a secondary source. The search included literature on skin barrier function in psoriasis, possible implications for managing psoriasis patients, and the use of nonprescription skincare, including cleansers and moisturizers as adjuncts to prescription treatment. Guidelines, consensus papers, and reviews published in English from 2010 to September 2022 were included in the search. Articles with no original data (except in cases where a review was the best available evidence), articles on prescription therapy alone (without discussion of nonprescription skin care), and publication language other than English were excluded from the search.

Search terms used: *Psoriasis AND skin barrier function(s); OR Psoriasis AND skin barrier dysfunction; OR Psoriasis AND skin lipids AND ceramides; OR Psoriasis prescription treatment AND cleansers; OR Psoriasis prescription treatment AND moisturizers; OR Psoriasis AND OTC skincare; OR psoriasis AND skincare efficacy, safety, tolerability.*

The searches yielded 41 clinically relevant papers (12 guidelines, algorithms, and consensus papers, 12 reviews, 2 randomized controlled trials, 8 clinical studies, 4 epidemiology, and QoI studies, and 3 other studies) to inform current best practices in psoriasis patients and skincare use. (Table 1 and Table 2). Robust comparative studies on skincare used as monotherapies or adjuncts to prescription topical and systemic therapies are scarce and did not allow for a systematic review.

RESULTS

In a workshop, the authors provided feedback on 15 statements created before the meeting and agreed upon 5 statements to offer expert guidance for gentle cleansers and moisturizer use in psoriasis patients.

Statement 1: *Inflammatory skin diseases are often associated with barrier defects, although the cause-and-effect relationship is complex in psoriasis and requires further studies.*

Psoriasis, an immune-mediated disease, is associated with comorbidities, such as psoriatic arthritis, metabolic syndrome, diabetes, and cardiovascular disease.[8] Psoriasis comprises multiple phenotypes that can be generalized or localized.[13,16-18] The pathophysiology of psoriasis is complex and includes many cytokines and signaling pathways[9-12] Research has led to insights into the psoriasis disease pathway, including the role of the tyrosine kinase 2 (TYK2) pathway.[19,20] The TYK2, a protein-coding gene, has been identified as part of the psoriasis susceptibility loci and is linked to interleukin (IL) -23 signaling.[19,20] TYK2 plays a critical role in the IL-23/IL-17 inflammatory axis, which is central to the pathophysiology of psoriasis.[11,19,20] Inflammatory skin diseases such as psoriasis are often associated with epidermal barrier dysfunction, although the cause-and-effect relationship is unclear and requires further studies.[9-12,16-22] Alterations to epidermal differentiation complex genes and several structures in the epidermal barrier in psoriasis may be responsible for the hyperproliferation of the epidermis in an attempt to repair the skin barrier.[10,16-22]

Stabilization of the skin barrier depends on intact keratinocytes and physiologic lipid synthesis. Depletion of ceramides in the stratum corneum has been reported in patients with psoriasis.[23-25] Animal studies and clinical studies that take skin biopsies from patients with psoriasis have suggested that ceramides play a relevant role in the pathophysiology of psoriasis.[23-25] However, data on moisturizers containing ceramides for psoriasis, either

TABLE 1.

Psoriasis and Skincare Studies

Reference	Type of Study	Population	Results
Wolf R, 2012[10]	Analysis of skin barrier structure and function	Hyperproliferative skin diseases, such as psoriasis.	Alterations in the epidermal barrier caused by derangement of lipids or ceramide synthesis may be one of the inducers of psoriasis.
Nakajima K, 2013[23]	A mouse model study	--	Barrier abnormality due to ceramide deficiency leads to psoriasiform inflammation.
Cho Y, 2004[24]	Samples from lesional and nonlesional epidermis obtained from psoriasis patients were analyzed	Korean patients with psoriasis	An inverse relationship between ceramide synthesis and clinical severity of psoriasis.
Hong KK, 2007[25]	A study on altered expression of serine palmitoyltransferase and ceramidase in psoriatric skin lesions	Psoriatic skin lesions	The ceramide-generating enzyme in the de novo synthesis in psoriatic epidermis, was significantly less than that of the nonlesional epidermis, which was inversely correlated with PASI score
Drealos ZD, 2008[32]	Open-label 4 week study of moisturizing cream in patients receiving topical psoriasis treatment	Mild-to-moderate plaque psoriasis (N=30)	NS TEWL change, increase skin hydration. Desquamation improved from very dry or normal. (P<0.0001 for all time points).
Del Rosso JQ, 2019[33]	Consumer usage study	Psoriasis	Ceramide- and keratolytic-containing body cleanser and cream application relieved psoriasis (84.8% of patients) and softened/smoothed skin (90.9%).
Liu M, 2015[34]	Randomized controlled trial T1: Combination of linoleic acid-ceramide moisturizer (LA-Cer) and mometasone furoate 0.1% cream (TCS) T2: Mometasone furoate monotherapy	Psoriasis vulgaris (N=106)	Topical application of a linoleic acid-ceramide-containing moisturizer showed benefits. Pruritus improved in both T1 and T2. T1 had better PASI-50 results at week 8 vs T2. T1 continued for another year with half of the patients with moisturizer and half only TCS. Less rebound and better skin condition in the combined TCS with moisturizer group.
Li X, 2020[39]	Multicenter, randomized, controlled trial on the efficacy and safety of a topical moisturizer containing linoleic acid and ceramide in combination with TCS	Mild-to-moderate psoriasis vulgaris (N=178)	After 4 weeks, improved skin condition. Maintenance with the moisturizer achieved a continuous improvement of BSA involvement, PASI score, investigators' assessment of skin dryness and desquamation, Physician Global Assessment of Psoriasis score, and patient QoL.
Man MQ, 2019[40]	Two self-controlled cohort studies. Both studies applied an emollient to one arm TID for 20 and 30 days and the other arm was not treated (control).	Psoriasis (n=30, and (n=60)	Delayed relapse on the treated arm was seen in 54.5% and 71% of patients in the first and second cohort, respectively.

BSA, body surface area; NS, not significant; QoL, quality of life; SA, salicylic acid; TEWL, transepidermal water loss; TCS, topical corticosteroids.

alone or in combination with other topical therapies, are limited and do not allow for evaluating possible clinical relevance.

Statement 2: *Guidelines and algorithms rarely mention skincare for psoriasis patients, demonstrating an important need gap.*

Guidelines and algorithms for psoriasis patients discuss prescription treatments.[11-15,20-22,26-29] There is a role for topical prescription therapy in all patients with psoriasis if the disease is limited (>5% body surface area), as a single treatment, and, in more extensive cases, as an adjunct therapy.[23,24] The main topical prescription classes are corticosteroids, Vitamin D3 analogs, combination steroids, vitamin D products, topical calcineurin inhibitors, topical retinoids, and a combination of topical steroids and retinoids.[23-29]

Topical prescription therapy can be combined with ultraviolet B (UVB) phototherapy (narrowband [NB] or broadband [BB]), or psoralen plus ultraviolet A (PUVA).[23-25] For more severe cases systemic treatment is available, such as with biologics (adalimumab, etanercept, infliximab, secukinumab, and ustekinumab.[23-27] One guideline mentioned salicylic acid-containing skincare added to topical or systemic therapy to remove scales. More robust data on skincare use are needed to have skincare incorporated into guidelines and pathways.

Statement 3: *Skincare may play a role in the management of psoriasis, regardless of disease severity or the therapy, both as adjuvant treatment of acute psoriasis and for follow-up treatment of healing skin during asymptomatic periods.*

TABLE 2.

Psoriasis Guidelines, Consensus Papers, and Algorithms Including Skincare With Gentle Cleansers and Moisturizers

Reference	Type of Study	Population	Results
Menter A, 2008[13]	Guideline	Psoriasis and psoriatic arthritis	Non-medicated moisturizers are applied 1 to 3 times a day. SA supports keratolysis, reduces scaling and softens plaques.
Hsu S, 2012[14]	Consensus guidelines	Plaque psoriasis	Non-medicated gentle cleansers and moisturizers and moisturizers with SA or urea soften plaques and improve the absorption of prescription topicals.
Elmets CA, 2021[15]	Guidelines for topical therapy and alternative medicine modalities	Psoriasis	Skincare as an adjunct to prescription topical treatment.
Navarini AA, 2017[16]	Consensus	Pustular psoriasis	Adjunctive skincare
Maul JT, 2021[26]	Swiss treatment pathway	Psoriasis	Adjunctive skincare with gentle cleansers and moisturizers. SA or urea-containing moisturizers to soften plaques.
Mrowietz U, 2011[28]	Consensus	Moderate to severe psoriasis	Adjunctive skincare with gentle cleansers and moisturizers.
Luger T, 2014[31]	Consensus	Psoriasis	Recommendations for adjunctive basic skincare.
Fluhr JW, 2008[32]	Review	Psoriasis	Recommendations for adjunctive moisturizers and keratolytic agents.
Menter A, 2009[13]	Guideline	Psoriasis	Traditional systemic treatments may be combined with non-medicated moisturizers or products with keratolysis.
Nast A, 2012[37]	Guideline	Psoriasis	Adjunctive skincare with gentle cleansers and moisturizers.
Jacobi A, 2015	Systematic review and recommendations	Psoriasis	Keratolytics and emollients have benefits for psoriasis.

SA, salicylic acid.

Clinically, moisturizers are well known for their role in hydration, moisture retention, and symptom control in psoriasis; however, these products may be underused.[14,15,26]

Published treatment guidelines on adjunctive skincare for psoriasis recommend gentle cleansers with a near physiologic stratum corneum pH[4-6] and moisturizers containing lipids and humectants.[28-33] Some authors suggest using keratolytic agents in the initial phase of treating psoriasis plaques and switching to moisturizing products and emollients in the intermediate and chronic/remission phases of psoriasis.[14,31] Keratolytics such as salicylic acid, urea, lactic acid, allantoin, glycolic acid, and trichloroacetic acid cause swelling and hydrolysis of skin to remove scales and calluses.[31] These keratolytics can irritate the skin, enhancing inflammation and potentially worsening the disease.[31] In a study of 30 patients with psoriasis who received a moisturizing cream for 4 weeks, skin hydration had increased with no change in transepidermal water loss measurements.[32] A significant percentage of patients showed improvements in desquamation measurements from very dry to dry or normal skin condition (P=.0001 for all time points).[32]

Two skincare products containing ceramides, salicylic acid, and urea (the first a body cleanser and the second a body cream) showed efficacy in a study of 33 patients with psoriasis.[33] Skin appearance overall had improved in 72.7% of patients who used body cream alone and in 75.8% of patients with the combination regimen of the body cream and the body cleanser. For the combined regimen, 84.8% reported that it provided relief from psoriasis, and 90.9% reported that their skin felt soft and smooth.[33]

The stratum corneum serves as an effective barrier against moisture loss.[9,24] Depletion of ceramides in the stratum corneum, which can result in increased moisture loss, has been reported in patients with psoriasis, leading to xerosis, which can benefit from skincare using gentle cleansers and moisturizers.[23-25]

Statement 4: *Studies of patients with psoriasis applying topical moisturizers showed softened plaques, enhancing the absorption of topical treatments such as corticosteroids.*

Epidermal barrier dysfunction is a clinically manageable feature of psoriasis.[33] Skincare, including gentle cleansers and moisturizers, is recommended for the prevention, treatment, and maintenance of psoriasis, together with prescription topical and systemic therapy.[14,34-37]

Ceramides are the predominant lipids in the stratum corneum, contributing to the intercellular lipid bilayer important for TEWL regulation. Ceramide-containing products promote a healthy skin barrier, reduce TEWL, and maintain stratum corneum hydration.[33,37] Keratolytics, such as salicylic acid and urea (a component of natural moisturizing factors), can be added to moisturizers to minimize xerosis, scaling, and hyperkeratosis.[33,37] Moreover, salicylic acid promotes a physiological stratum corneum pH.[38]

Moisturizers have shown benefits when used as adjunctives to prescription treatment. A study of a ceramide-containing moisturizer applied in combination with topical prescription treatment with mometasone furoate 0.1% cream demonstrated less psoriasis relapse than topical therapy alone.[34]

Although the benefits of adjunctive skincare application have been reported in small studies and clinical reviews, the panel recognized the need to develop a more robust body of evidence to influence clinical practice in a meaningful way. Nevertheless, the panel members agreed that incorporating skincare principles into the psoriasis paradigm may evolve into the standard of care and be included in future treatment guidelines.

Statement 5: *Studies applying ceramides-containing skincare showed an overall improvement in the appearance of the skin and provided relief for psoriasis. These results suggest that improvements in epidermal function with topical emollients can prevent/attenuate the development of psoriasis.*

A common clinical feature of psoriasis is the scaling typically associated with hyperkeratosis, pruritus, inflammation, and xerosis.[9,15,24] Moisturizers promote moisture retention in the stratum corneum and can help reduce pruritus and desquamation.[15]

Topical moisturizers in psoriasis have been reported to increase hydration, decrease desquamation, improve the skin's overall appearance, improve Psoriasis Area and Severity Index (PASI)-50 in conjunction with topical steroids, and delay relapse. In a randomized controlled study of 106 patients with psoriasis, the treatment group (T1) received a combination of linoleic acid-ceramide moisturizer and mometasone furoate 0.1% cream) and the control group (C1) received mometasone furoate monotherapy.[34] Improvement in pruritus was observed in both groups after 4 weeks. The treatment group reported superior PASI-50 results at week 8 compared with the control group. Higher water content and earlier reduction of lesional transepidermal water loss (TEWL) were observed in T1 vs C1. Subsequently, T1 patients were randomized for another year to 2 groups: T2 received a combination of linoleic acid-ceramide moisturizer and mometasone furoate 0.1% cream, and the control group (C2) did not receive a moisturizer. After one year, less relapse of psoriasis was observed in T2 compared with C2.[34] Lesional TEWL, water content, and PASI measurements remained stable in T2 patients.[34] In a second multicenter, randomized, controlled trial of 178 patients with psoriasis, treatment with mometasone furoate combined with a linoleic acid-ceramide-containing moisturizer for 4 weeks resulted in decreased rates of relapse.[39]

Maintenance therapy with linoleic acid-ceramide-containing moisturizer demonstrated continuous improvement in body surface area (BSA) involvement, PASI score, investigators' xerosis and desquamation assessment, Physician Global Assessment of Psoriasis score, and patient QoL.[39]

Patients with mild plaque psoriasis, seborrheic dermatitis, sebo-psoriasis, or persistent post-psoriasis sequelae may experience some symptom improvement even without prescription therapy when compliant with a rigorous moisturization regimen.[39]

In a study of psoriasis relapse prevention with ceramide-based adjunctive skincare, 2 cohorts of patients with psoriasis (n=30 and n=60) were treated topically with a proprietary emollient ceramide-based cream applied twice daily to one forearm.[40] The same sites on the contralateral arm served as the untreated control. A delayed relapse on the treated arm was observed in 54.5% of patients in the first cohort (20 days of use) and 71% of patients in the second cohort (30 days of use).[40] These results suggest that using moisturizers to promote a healthy skin barrier may prevent or attenuate psoriasis flares.

Limitations

A detailed discussion of the pathophysiology of psoriasis is outside this review's scope.

Despite the widespread availability of nonprescription skincare products, there are few robust evidence-based studies on skincare for psoriasis patients.

CONCLUSION

The literature published on skincare in psoriasis is limited compared with other common skin conditions with known barrier defects. Topical moisturizers have shown several benefits in psoriasis, such as improved hydration and overall skin appearance, increased attainment of PASI-50, decreased desquamation, and delayed relapse.

Clinicians and patients would benefit from increased awareness of the importance of skincare in psoriasis. Early initiation and maintenance of well-tolerated treatment regimens and the use of carefully selected adjunctive skincare are potential considerations for increasing patient compliance and outcomes.

DISCLOSURES

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All the authors developed the manuscript, reviewed it, and agreed with its content.

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ORIGINAL ARTICLE

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Tapinarof, a Novel, First-in-Class, Topical Therapeutic Aryl Hydrocarbon Receptor Agonist for the Management of Psoriasis

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ABSTRACT

Topical treatments remain the foundation of psoriasis management. Tapinarof (VTAMA®; Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults and is under investigation for the treatment of psoriasis in children, and atopic dermatitis in adults and children down to 2 years old. Here, we review the mechanism of action of tapinarof and the PSOARING phase 3 trial program in mild to severe psoriasis. AhR is a ligand-dependent transcription factor involved in maintaining skin homeostasis. Tapinarof specifically binds to AhR to decrease proinflammatory cytokines, decrease oxidative stress, and promote skin barrier normalization. In two identical, randomized, 12-week pivotal phase 3 trials, PSOARING 1 and 2, tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe psoriasis. In the PSOARING 3 long-term extension trial of repeated, intermittent tapinarof cream in eligible patients completing the pivotal trials, a high rate of complete disease clearance (40.9%) and a remittive effect of approximately 4 months off therapy were demonstrated over 52 weeks, with no tachyphylaxis. The most common adverse event, folliculitis, was mostly mild or moderate and resulted in a low trial discontinuation rate in PSOARING 1 and 2 (≤1.8%). Tapinarof cream 1% QD provides a novel, non-steroidal, topical treatment option for patients with psoriasis and is highly effective and well tolerated with long-term use including when applied to sensitive and intertriginous skin.

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INTRODUCTION

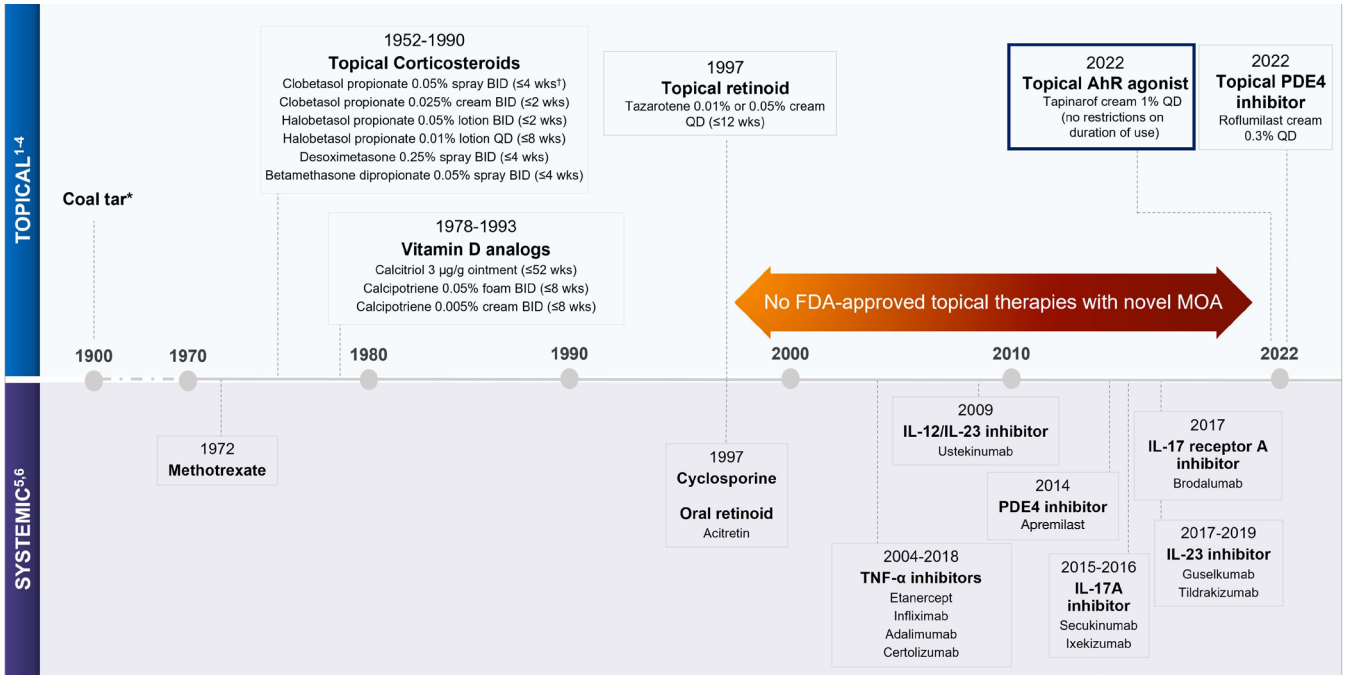
Current Treatments and Unmet Needs in Psoriasis

Psoriasis is a chronic, immune-mediated skin disease that affects approximately 8 million adults in the Unite States and 2% to 3% of people worldwide.[1-3] Psoriasis is characterized by scaly, erythematous, pruritic plaques that can be painful and unsightly, with itch being the most prevalent and burdensome symptom.[2,4] Although skin manifestations are the hallmark of psoriasis, it is considered to be a systemic inflammatory disease that often coexists with conditions such as psoriatic arthritis, obesity, and cardiovascular and psychiatric complications.[2,5,6] The significant physical, psychological, and socioeconomic burdens experienced by patients with psoriasis can include an increased risk of anxiety, depression, and suicidal ideation.[6-8]

Psoriasis is primarily managed by dermatologists, nurse practitioners, and physician assistants specializing in dermatology, and also by rheumatologists and primary care physicians. Treatment is guided by disease severity measured by the extent and location of skin affected (eg, using the Physician Global Assessment [PGA]), and by evaluation of patients' own experiences.[9]

Most patients with plaque psoriasis have mild to moderate disease, and topical therapy is considered to be an appropriate treatment.[5,10,11] In addition to their use in mild to moderate disease, topical therapies are often used as adjunctive treatment regardless of disease severity.[11] Treatments indicated for moderate to severe psoriasis include oral systemic medications

FIGURE 1. History of innovation in psoriasis therapy based on FDA approval in the US, including approved dosing regimen and restrictions regarding duration of use for topical agents.



*Available in the US (not approved by the FDA). †Greater than 2 weeks of treatment is limited to localized moderate/severe lesions that insufficiently improve.
AhR, aryl hydrocarbon receptor; BID, twice per day; FDA, US Food and Drug Administration; IL, interleukin; MOA, mechanism of action; PDE4, phosphodiesterase 4; QD, daily; TNF, tumor necrosis factor; wks, weeks.
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(eg, methotrexate, cyclosporine, apremilast, deucravacitinib, and acitretin), biologic therapies (including inhibitors of tumor necrosis factor-alpha, interleukin [IL]-12/IL-23, IL-23, and IL-17), and phototherapy.[5,9,12,13] Certain topical therapies are associated with restrictions on duration, extent, and site of application, and with local irritation and other adverse events (AEs).[11] Adherence challenges and low patient satisfaction with topical therapies can also be due to frequency and difficulty of application, the associated time burden, and properties of the formulation and vehicle, such as texture and odor.[14-16]

Here, we review the development of tapinarof (VTAMA®; Dermavant Sciences, Inc.), a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration (FDA) in May 2022 for the treatment of plaque psoriasis in adults, and under investigation for the treatment of psoriasis in children down to 2 years of age and for atopic dermatitis (AD) in adults and children down to 2 years of age.

History of Psoriasis Treatments

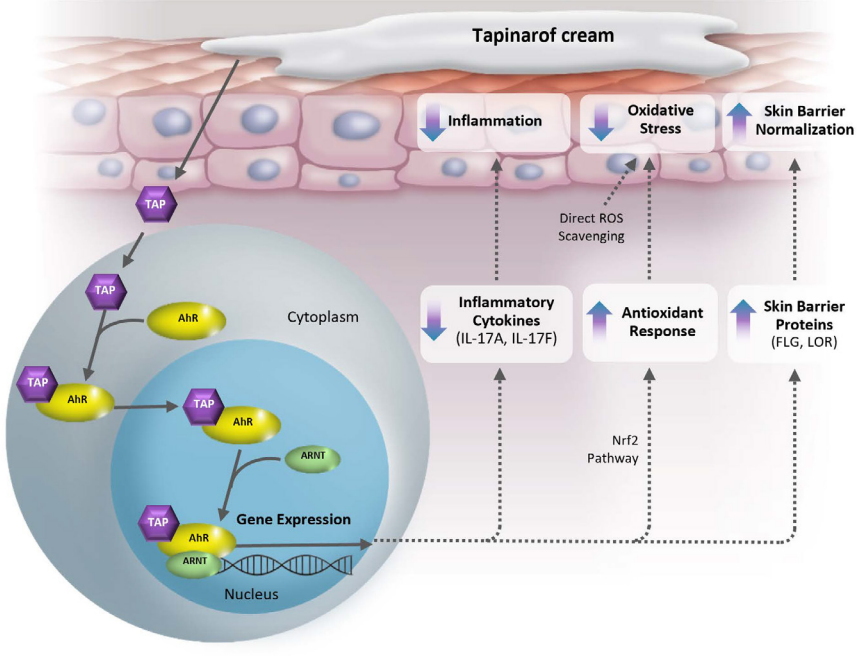
Progress in the development of psoriasis treatments over the last 50 years is summarized in Figure 1. Until recently, the only FDA-approved topical treatments for psoriasis were corticosteroids, vitamin D analogs, and retinoids.[11,17] Although these therapies may be efficacious, especially for short-term treatment of localized disease, they have limitations based on affected body surface area, duration of use, and location of application.[11] Use of corticosteroids may also be limited by the potential for skin atrophy, recurrence of symptoms after cessation of treatment, tachyphylaxis, and patient and/or prescriber aversion/fear of their use.[11,18] Other topical agents, including calcipotriene and tazarotene, have modest efficacy as monotherapies and well-documented AEs, including erythema and skin irritation.[11,19]

NOVEL TOPICAL THERAPY

Development of Tapinarof

The discovery of tapinarof was a fortuitous outcome of investigations into secondary metabolites of a bioluminescent bacterium, *Photorhabdus luminescens*, which lives symbiotically in soil-living nematode worms that parasitize insects.[17] Insects infected by the nematodes did not decay after death and the investigator hypothesized that metabolites produced by the bacteria were responsible for this effect.[17] One metabolite was purified and identified as 3,5-dihydroxy-4-isopropylstilbene (tapinarof), which demonstrated anti-inflammatory properties

FIGURE 2. Proposed mechanism of action of tapinarof in plaque psoriasis.



AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; IL, interleukin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof. Bissonnette R, et al. *J Am Acad Dermatol.* 2021;84:1059-1067.

and potent binding to AhR.[17,20] Tapinarof is now synthetically produced and formulated in a topical cream.[21,22]

The Aryl Hydrocarbon Receptor Pathway and Tapinarof Mechanism of Action

AhR is a transcription factor expressed by various cell types, including immune cells and epithelial cells in barrier tissues such as skin, gastrointestinal tract, and lungs.[23] In the skin, AhR helps maintain homeostasis by mediating responses to chemical and environmental challenges. Transcription factors such as AhR regulate gene expression and directly mediate diverse effects by binding to specific DNA sequences. AhR can be activated by a wide range of molecules (ligands) found in endogenous, dietary, environmental, and microbial sources.[23] An important characteristic of AhR is its differential activation by a wide range of ligands, which elicits induction or suppression of various genes resulting in diverse signaling and biologic responses.[17] AhR can also signal through other transcription factors, leading to varied biologic effects that are highly dependent on the specific ligand.[23,24]

AhR has been shown to regulate the expression of T-helper (Th) 17 and Th22 immune cells, and IL-17 and IL-22 cytokines, which are implicated in psoriasis.[25] AhR is also implicated in Th2 cell differentiation, and IL-4 and IL-5 production, which are important in the pathogenesis of AD.[26] Furthermore, impaired skin barrier function in psoriasis and AD is associated with downregulation of skin barrier proteins (filaggrin, loricrin, and involucrin); these proteins are upregulated by AhR activation and signaling.[24]

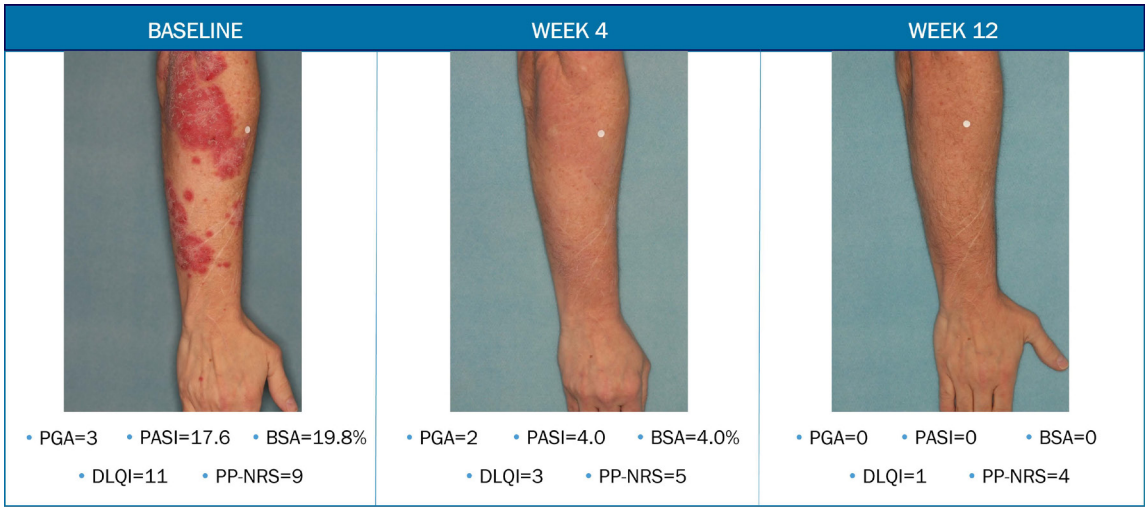
The proposed mechanism of action of tapinarof in psoriasis is shown in Figure 2. Once tapinarof binds to AhR, the tapinarof–AhR complex moves to the nucleus and binds to the AhR nuclear translocator (ARNT), creating a high-affinity DNA-binding transcription factor.[17,23,24] The tapinarof–AhR/ARNT complex binds to specific DNA recognition sites of AhR-responsive genes and modulates gene expression.[23,24]

The unique clinical profile of tapinarof results from specific binding to AhR. Tapinarof binds to and activates AhR to downregulate pro-inflammatory cytokines implicated in psoriasis (IL-17A and IL-17F), which most likely contributes to its rapid therapeutic benefit.[20] Additionally, tapinarof-activated AhR decreases oxidative stress through the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway; and the tapinarof molecule directly scavenges reactive oxygen species (Figure 2).[20] Tapinarof also promotes skin barrier normalization by increasing skin barrier proteins related to keratinocyte differentiation, including filaggrin and loricrin.[17,20]

Tapinarof Cream for Psoriasis and Atopic Dermatitis

The PSOARING phase 3 trial program that evaluated tapinarof cream to treat plaque psoriasis in adults launched in 2019 with two identical, multicenter, double-blind, vehicle-controlled trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980), followed by the long-term extension trial, PSOARING 3 (NCT04053387).[22,27] The ADORING phase 3 trial program of tapinarof cream for the treatment of AD in adults and children began in 2021.[28]

FIGURE 3. Clinical response of a patient with plaque psoriasis treated with tapinarof cream 1% QD who achieved primary and secondary efficacy endpoints at week 12 in the PSOARING 1 clinical trial. PGA and PASI are global efficacy assessments. Example of one representative target lesion of one tapinarof-treated patient from PSOARING 1 clinical trial.



BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

Efficacy of Tapinarof Cream for Psoriasis

Tapinarof cream 1% once daily (QD) demonstrated statistically significant efficacy vs vehicle and was well tolerated in adults with mild to severe plaque psoriasis in the two 12-week, pivotal phase 3 trials, PSOARING 1 (N=510) and PSOARING 2 (N=515).[22] Eligible patients had a PGA score of 2 (mild) to 4 (severe) and a percentage body surface area (%BSA) affected of 3% to 20% at baseline. Patients were randomly assigned 2:1 to tapinarof cream or vehicle cream QD for 12 weeks, after which eligible patients could enroll in PSOARING 3. The primary endpoint was PGA response, defined as a PGA score of 0 (clear) or 1 (almost clear), and a decrease of at least 2 points from baseline at week 12. This was achieved by a significantly higher proportion of patients in the tapinarof group vs vehicle in PSOARING 1 and 2: 35.4% vs 6.0% and 40.2% vs 6.3%, respectively (both $P<0.0001$).[22,29] All secondary efficacy endpoints were met for tapinarof cream vs vehicle in PSOARING 1 and 2 ($P\leq0.0005$). These included: the proportion of patients with a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI75) at week 12 (36.1% vs 10.2% and 47.6% vs 6.9% in PSOARING 1 and 2, respectively); the proportion with a PGA score of 0 or 1 at week 12 (37.8% vs 9.9% and 43.6% vs 8.1%); the mean change from baseline in %BSA affected at week 12 (–3.5% vs –0.2% and –4.2% vs 0.1%); and the proportion with a reduction of at least 90% in the PASI score (PASI90) at week 12 (18.8% vs 1.6% and 20.9% vs 2.5%).[22,29,30] Figure 3 shows a patient treated with tapinarof cream who achieved primary and secondary efficacy endpoints at week 12.

Improvements with tapinarof cream were seen as early as the first clinical assessment at week 2 and continued to week 12; additional efficacy was achieved in the long-term extension trial, PSOARING 3.[30] The efficacy of tapinarof cream was consistent across a broad spectrum of disease severity (as evaluated by PGA score, %BSA affected, and duration of disease) and patient demographics (including sex, age, race, and country of enrollment [US or Canada]).[31]

PSOARING 3 assessed the safety, efficacy, and tolerability of tapinarof cream 1% QD, as well as durability of response on therapy (absence of tachyphylaxis), and duration of remittive effect off therapy.[27] Patients received up to 40 weeks of open-label treatment followed by 4 weeks of follow-up off treatment. Therefore, patients could be treated with up to 52 weeks of tapinarof from PSOARING 1 and 2 baseline through PSOARING 3 completion.[27]

In PSOARING 3, patients were treated based on their PGA score. Those entering the trial with PGA≥1 received tapinarof cream until complete disease clearance was achieved (PGA=0). Patients entering with, or achieving, PGA=0 discontinued treatment and were monitored for the duration of remittive effect, defined as off-therapy maintenance of PGA=0 or 1. Patients with PGA≥2 were treated or re-treated until PGA=0.

In total, 91.6% (n=763) of eligible patients completing PSOARING 1 and 2 elected to enroll in PSOARING 3. Overall, 40.9% (n=312) achieved complete disease clearance (PGA=0) at least once during the trial. Among patients entering with PGA≥2, 58.2% (n=302) achieved PGA=0 or 1. Among patients achieving PGA=0 at any time during the trial (n=312), the mean total duration of remittive effect off treatment was approximately 4 months

(130 days). For patients entering the trial with PGA=0 (n=79), the median duration of remittive effect off treatment was also approximately 4 months (115 days). Durability of response on treatment (ie, no tachyphylaxis) of up to 52 weeks was observed. Treatment with tapinarof cream in PSOARING 1 and 2 resulted in rapid, clinically meaningful, and statistically significant improvements in patient-reported outcomes. This included itch as measured by the Peak Pruritus Numerical Rating Scale, quality of life measured by the Dermatology Life Quality Index (DLQI), and psoriasis symptoms and functional health measured by Psoriasis Symptom Diary scores.[32] Continued and durable improvement in quality of life (DLQI) was demonstrated in PSOARING 3.[33]

Safety and Tolerability of Tapinarof Cream in Psoriasis

Tapinarof cream 1% QD was well tolerated with long-term use up to 52 weeks as reported by patients and investigators, including when applied to sensitive and intertriginous skin areas.[27]

Most treatment-emergent AEs in PSOARING 1 and 2 were mild or moderate in severity and did not lead to trial discontinuation.[22] The most common treatment-emergent AEs overall were folliculitis, nasopharyngitis, and contact dermatitis.[22] AEs of special interest, identified from phase 2 trials, were folliculitis, contact dermatitis, and headache, which were mostly mild or moderate. Tapinarof has a role in regulating skin barrier protein expression; consequently, tapinarof-induced folliculitis may involve follicular cornification and plugging following upregulation of components of the stratum corneum associated with keratinocyte differentiation.[24,34] Therefore, folliculitis may be an 'on-target' effect of topical tapinarof, is generally mild and self-limiting, and does not interfere with therapy.[35] There was only one severe (grade 3) event each of folliculitis, contact dermatitis, and headache occurring across the phase 3 PSOARING program with up to 52 weeks of treatment. Trial discontinuation rates due to AEs of special interest were low in PSOARING 1 and 2 (≤1.8%, ≤2.0%, and ≤0.6% for folliculitis, contact dermatitis, and headache, respectively) and PSOARING 3 (1.2%, 1.4%, and 0%, respectively).[22,27]

Patient Satisfaction with Tapinarof Cream for Psoriasis

In PSOARING 3, patient satisfaction with efficacy, formulation elegance, application ease, impact on daily life, and preference for tapinarof vs prior therapies was assessed at week 40 (or early termination) using a Patient Satisfaction Questionnaire®.[36] Most patients either strongly agreed or agreed that they could easily manage their psoriasis with tapinarof (85.8%), were satisfied with how well tapinarof worked (83.6%), felt that tapinarof cleared their skin and prevented psoriasis from returning (62.9%), had confidence in tapinarof (84.1%), would recommend tapinarof to other patients with psoriasis (84.0%), and would use tapinarof again or continue tapinarof if it was available (82.5%). Most patients were satisfied with the time spent applying tapinarof (93.2%) and felt that tapinarof was easy to apply (96.3%), was quickly absorbed (89.5%), felt good on their skin (79.9%), was not greasy (89.0%), and were satisfied with the look and feel of tapinarof (87.7%). In patients who had previously used other topical agents and those who had used systemic drugs, the majority considered tapinarof more effective, easier to use, and preferred versus previous agents.

Clinical Use of Tapinarof Cream to Treat Plaque Psoriasis

Patients should be advised to apply tapinarof cream as a thin layer once daily to affected areas.[37] Tapinarof cream has no warnings, restrictions on location of application or duration of use, precautions, contraindications, or drug interactions; it is not for oral, ophthalmic, or intravaginal use.[37] Pharmacokinetic evaluation of topical tapinarof in patients with psoriasis has demonstrated minimal systemic exposure, which supports the absence of restrictions and of drug–drug interactions.[24,34,37]

CONCLUSION

Tapinarof cream 1% QD is a novel, non-steroidal topical treatment that binds to a distinct site on AhR, creating unique biological outcomes that manifest clinically as therapeutic disease control for patients with psoriasis. The proposed mechanism of action includes decreasing pro-inflammatory cytokines, decreasing oxidative stress, and promoting skin barrier normalization. The remittive effect demonstrated in the long-term extension trial may be attributed to the additional roles of AhR in modulating T-cell responses that are a major component of psoriatic lesions.[38]

Tapinarof cream was efficacious and well tolerated in adult patients with mild, moderate, or severe plaque psoriasis, including on sensitive and intertriginous skin areas, and demonstrated an approximately 4-month remittive effect off therapy and no tachyphylaxis on therapy with long-term use. The most common AE was folliculitis, which was mostly mild or moderate in severity, likely representing an 'on target' effect of tapinarof, and resulted in few trial discontinuations. Tapinarof cream 1% QD is a new topical treatment indicated for patients with plaque psoriasis with no restrictions regarding duration of use, application site, concomitant therapies, and extent of body surface area affected.

DISCLOSURES

Margaret Bobonich has served as a speaker and/or consultant for AbbVie, Boehringer Ingelheim, Biofrontera, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Novartis, and UCB Biopharma.

Joe Gorelick has served as a consultant and/or speaker for AbbVie, Bristol Myers Squibb, Eli Lilly, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Sun Pharmaceuticals, and UCB Biopharma.

Lakshi Aldredge has served as a speaker and/or consultant and/or involved in advisory boards for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Dermavant Sciences Inc, Eli Lilly, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB Biopharma.

Matthew J. Bruno has served as a consultant, and/or received payment for promotional presentations from AbbVie, Almirall, Bristol Myers Squibb, Dermavant Sciences, Inc., EPI Health, Journey Medical Corporation, Mayne Pharma, Medimetriks Pharmaceuticals, Pfizer, Regeneron/Sanofi-Genzyme, and Sun Pharmaceuticals.

Douglas DiRuggiero has served as a speaker and/or has been involved in advisory boards for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, EPI Health, Eli Lilly, Incyte, Novartis, Regeneron, Sanofi, Sun Pharmaceuticals, and UCB Biopharma.

George Martin has served as a speaker and/or consultant and/or has been involved in scientific advisory boards for AbbVie, Almirall, Arcutis, Biofrontera, Bristol Myers Squibb, Dermavant Sciences, Inc., DUSA/SUN, Eli Lilly, Evelo, Galderma, Horizon, Incyte, Janssen, LEO Pharma, Ortho/Bausch Health, Organogenesis, Pfizer, Sanofi/Regeneron, Trevi, and UCB Biopharma.

Anna M. Tallman is an employee of Dermavant Sciences Inc., with stock options.

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ORIGINAL ARTICLE

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Hormonal Treatments in Hidradenitis Suppurativa: A Systematic Review

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is an inflammatory skin condition characterized by recurrent abscesses, nodules, and sinus tracts. Hormones are thought to play an important role in HS pathophysiology, but there is a lack of an updated review on hormonal treatments in HS.

Objective: Perform a systematic review of the literature on hormonal treatments in patients with HS.

Methods: In April 2022, MEDLINE and EMBASE databases were searched for articles on hormonal treatments in HS. Non-English, duplicate, and irrelevant results were excluded. Data extraction was performed by two reviewers.

Results: From 1952 to 2022, 30 articles (634 patients) met the inclusion criteria. Anti-androgen treatments discussed include finasteride (n=8), spironolactone (n=7), cyproterone acetate (CPA) (n=5), flutamide (n=1), leuprolide (n=1), and buserelin acetate (n=1). Metabolic treatments reported include metformin (n=8) and liraglutide (n=2). Three articles on hormonal contraceptives and 2 articles on testosterone were included. Of the articles which reported response rates, 62.8% (27/43) of patients improved with finasteride, 53.3% (32/60) with CPA mono/combination therapy, 50.5% (51/101) with spironolactone, and 46.0% (74/161) with metformin. Improvement in HS was also noted in case reports of patients treated with buserelin acetate, leuprolide, flutamide, and liraglutide.

Conclusions: Hormonal treatments for HS, especially finasteride, spironolactone, and metformin, are efficacious and safe; but large-scale randomized controlled trials are needed to determine the patient populations which would benefit from these therapies.

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INTRODUCTION

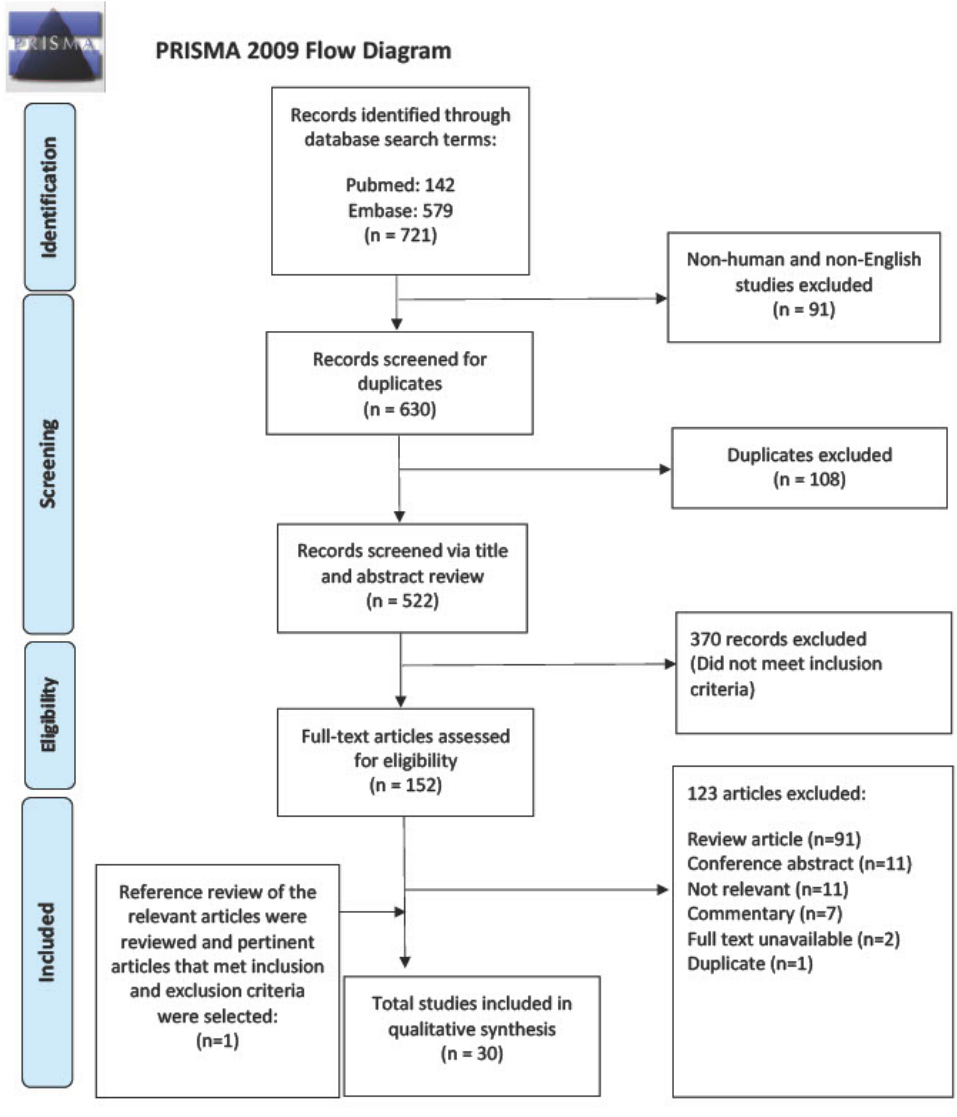
Hidradenitis suppurativa (HS) is a chronic, oftentimes debilitating inflammatory skin condition characterized by abscesses, inflammatory nodules, sinus tracts, and scarring.[1] Existing data suggest multifactorial etiology with genetic, hormonal, and immune dysregulating factors.[1] A hormonal component to HS is supported by typical onset of disease after puberty, fluctuations in disease activity during menses and pregnancy, and HS comorbidities such as metabolic syndrome and polycystic ovarian syndrome (PCOS).[2-6] Given that women of child-bearing age are disproportionately affected by HS,[7] understanding the effects of different hormonal treatments on HS symptoms is critical. Herein, we conducted a systematic review to evaluate existing literature on the efficacy and safety of hormonal therapies in HS.

MATERIALS AND METHODS

Search Strategy

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was pre-registered on PROSPERO (CRD42021283596). On April 25, 2022, two independent reviewers (RM and CJ) searched MEDLINE and EMBASE databases from inception to search date with the following terms: ("hidradenitis suppurativa" OR "hidradenitis" OR "acne inversa" OR "Verneuil disease" OR "Velpeau disease") AND ("hormone" OR "hormonal" OR "estrogen" OR "progesterone" OR "progestin" OR "testosterone" OR "antiandrogen" OR "metformin" OR "spironolactone" OR "contraceptive" OR "finasteride" OR "cyproterone acetate" OR "dutasteride" OR "intrauterine device" OR "medroxyprogesterone acetate" OR "clascoterone").

FIGURE 1. PRISMA flow diagram.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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A total of 721 articles were identified. Articles were filtered to remove non-English language and non-human studies. Duplicate articles were excluded. Titles and abstracts were screened for relevance. Full text review was then manually performed on the remaining 152 articles by the two independent reviewers (RM and CJ). Studies where hormonal interventions were the primary study intervention were considered eligible for inclusion. Reviews, conference abstracts, meta-analyses, commentaries, non-relevant articles, and articles with no full-text available were excluded. Any discrepancies were discussed to consensus with a third reviewer (TS). Reference lists of articles that met inclusion criteria were screened for additional relevant articles and 1 additional article was identified.

Data Extraction

Two reviewers (RM and CJ) independently completed data extraction. Any discrepancies were discussed to consensus with a third reviewer (TS). For each article, the study design, country of study, patient demographics, HS severity, study intervention, efficacy outcomes, and safety outcomes were recorded. Articles were assessed for quality utilizing Cochrane Risk of Bias for prospective trials,[8] Newcastle-Ottawa Scale (NOS) for cohort studies,[9] and modified NOS for cross-sectional studies.[10]

RESULTS

Thirty articles published between 1952 to 2022 fit the aforementioned search criteria and were included in this review

(Figure 1). There was a total of 634 patients. Study design, patient demographics, interventions, previous treatments, concomitant treatments, response, and adverse effects of the final studies are reported in Table 1 and Table 2.

Anti-androgen interventions include finasteride (n=8), spironolactone (n=7), cyproterone acetate (CPA) (n=5), flutamide (n=1), leuprolide (n=1), buserelin acetate (n=1). Interventions targeting the insulin pathway include metformin (n=8) and liraglutide (n=2). Three articles discuss hormonal contraceptives. Two articles on testosterone propionate and testosterone cypionate are included.

Age at the time of study ranged from 6 to 88 years. Hurley stage was reported in 9 studies (193 patients, 18.1% Hurley I, 60.6% Hurley II, 21.2% Hurley III). Study locations include United States (n=10), United Kingdom (n=6), Canada (n=3), Ireland (n=3), Spain (n=2), India (n=1), Portugal (n=1), Netherlands (n=1), China (n=1), Australia (n=1), and Italy (n=1). There were 18 case reports/series, 8 retrospective cohort studies, 3 prospective trials, and 1 cross sectional study. In terms of study quality, 2 of the 3 trials had a high risk of bias and 1 had an unclear risk of bias. Of the 8 retrospective cohort studies, 1 was good quality and 7 were poor quality. The cross-sectional survey study was rated as poor quality.

Anti-Androgen Treatments

Finasteride

Of the articles which reported a response rate, 62.8% (27/43) of patients improved with finasteride therapy. Of patients with reported disease severity, 9 had Hurley stage I disease, 8 stage II, and 7 stage III. Across 5 case reports/series with 13 patients total, clinical improvement was seen in 92.3% of patients.[11-15] In one of the case series, finasteride was prescribed concurrently with oral contraceptives in 2 patients and antibiotics in 3 patients.[14] Finasteride use in HS has been studied in the pediatric population. In Mota et al's case series from 2017, 5 patients aged 6-11 exhibited a complete response to therapy, and remission was maintained in 4 patients for 5 to >24 months. Similarly, Randhawa et al reported that 3 pediatric patients aged 7, 15, and 15, treated with finasteride had a reduction in the frequency and severity of their flares.

In 2005, Joseph et al conducted a prospective trial that analyzed the effects of 5 mg of finasteride daily in 7 patients. After 6-16 weeks of treatment, 3 patients had complete resolution of disease and 3 had a partial response.[16] In Collier et al's survey study, 1 of 3 patients reported improvement with finasteride.[3] More recently, in Babbush et al's 2022 retrospective cohort study of 20 patients, 40% of patients self-reported improvement on 5 mg of finasteride daily and 50% of patients were satisfied with the drug.[17] Side effects of finasteride reported amongst HS patients include breast tenderness, nausea, menstrual irregularities, headache, sexual dysfunction, generalized pruritis, and rash.[16,17]

Spironolactone

About half (50.5%, 51/101) of patients responded to spironolactone based on 4 studies that provided a response rate.[18,19] Where data on disease severity were reported, 7 patients had Hurley stage I disease, 54 patients stage II, and 7 patients stage III. In a retrospective case series by Lee and Fischer, the majority of the 20 patients were on spironolactone 100 mg daily for 3 months. Complete resolution of disease was observed in 55% of patients and 30% had a partial response.[19] This study also included 3 adolescent HS patients aged 14, 15, and 17, all of whom reported improvement. In Golbari et al's retrospective cohort study, 46 HS patients received an average dose of 75 mg spironolactone daily; substantial improvements were noted in pain scores, lesion counts, and Hidradenitis Suppurativa-Physician Global Assessment (HS-PGA) scores at a mean follow up time of 7.1 months.[20] McPhie et al described 12 patients on spironolactone 100 mg daily and 41.7% of patients had an improved International Hidradenitis Suppurativa Severity Score System (IHS4) score.[18] In a retrospective cohort study of 26 patients on spironolactone 50 mg or 100 mg daily, Quinlan et al found that mean lesion count and DLQI improved significantly.[21] Collier et al reported that 42.4% (28/66) of surveyed patients improved on spironolactone.[3] On the other hand, spironolactone was only beneficial for 1 out of 3 patients in a retrospective study by Kraft and Searles.[22] Overall, spironolactone was well-tolerated in HS patients but the side effects reported include nausea, dizziness, gastrointestinal upset, altered mood, breast tenderness, and changes in urination.[18,19,21] Two patients were reported to have discontinued spironolactone due to gastrointestinal upset.[21]

Buserelin, Leuprolide, and Flutamide

In one case report, a patient with HS on buserelin acetate, a luteinizing hormone agonist, 0.21 mg thrice daily experienced remission for 10 months.[23] In another case report, a patient on leuprolide, a gonadotropin-releasing hormone (GnRH) agonist, 1 mg daily experienced marked improvement in vulvar and perineum lesions.[24] A case report of a patient on flutamide, an androgen receptor antagonist, 250 mg daily described marked improvement in lesions at 2 months and decreased frequency and severity of flares 1 year after the dose was decreased to 125 mg daily.[25] Patients on buserelin acetate and leuprolide endorsed mild and infrequent vasomotor symptoms.[23,24]

Hormonal Contraceptives

In 1989, Stellon and Wakeling reported a case series of 7 patients who developed HS while on oral contraceptive pills (OCPs). Three of the patients benefited from a change to a combined pill containing a higher estrogen: progestogen ratio and 2 reported complete resolution of the disease after discontinuing OCPs. One patient continued to have relapses while on progestogen-only pills.[26] A cross-sectional study by Collier et al reported a trend towards a greater response to OCPs in respondents with menstrual HS flares compared to those without flares (24.5% vs 10%; P= 0.087).[3] Peterson et al conducted a retrospective cohort

TABLE 1.

Anti-Androgen Treatments for Hidradenitis Suppurativa

Study reference	Intervention	Patient characteristics	Treatment response and adverse effects	Response timepoint	Study quality^
Finasteride					
Babbush et al 2022; US; Retrospective cohort	Finasteride 5 mg/d	n=20F, Mean age=34.3 ± 13.5 Hurley I (n=4), II (n=6), III (n=7) PFT: spironolactone; CT: topical (n=19)/oral (n=12) abx, biologics (n=11)	Pt assessment: 40% (8/20) improved, 60% (12/20) neutral Pt satisfaction: 50% (10/20) satisfied, 35% (7/20) neutral, 15% (3/20) dissatisfied 90% (18/20) willing to take finasteride again AE: nausea (n=2), menstrual irregularities (n=2), headache (n=1), breast tenderness (n=1), sexual dysfunction (n=1)	Not reported	Poor quality Total: 4/9 Selection: 3/4 Comparability: 0/2 Outcome: 1/3
Buonomo et al 2021; US; Case series	Finasteride 5 mg/d	n=2M (transgender) Pt 1: Age=30, Hurley II; Pt 2: Age=40, Hurley II PFT: abx, isotretinoin, ADA, ILK, systemic steroid; CT: MHT (n=2), topical BP and clindamycin (n=1)	Pt 1: Discontinued at 2mo d/t worsening depression Pt 2: Stable disease AE: worsening depression (n=1)	Up to 1.5y	--
Collier et al 2020; US; Cross-sectional	Finasteride	n=4F	Improved: 33.3% (1/3) Unchanged: 66.7% (2/3)	Not reported	Poor quality Total: 5/10 Selection: 3/5 Comparability: 0/2 Outcome: 2/3
Doménech et al 2012; Spain; Case report	Finasteride 5 mg/d	n=1M, Age=28 PFT: oral abx, isotretinoin, IFX, etanercept	Near complete remission	1y	--
Farrell et al 1999; UK; Case series	Finasteride 5 mg/d	n=2 (1M, 1F), Ages=56 (M), 55 (F) PFT: CPA	Improved: 100% (2/2)	1-9mo	--
Joseph et al 2005; India; Prospective trial	Finasteride 5 mg/d	n=7 (5F, 2M), Ages=16-35 Moderate (n=5), severe (n=2) PFT: abx; CT: abx stopped in 1st week (n=2)	Complete response: 42.9% (3/7) Partial response: 42.9% (3/7) Recurrence in 28.6% (2/7) 1mo after stopping finasteride but responded to re-introduction AE: breast enlargement and tenderness (n=2), pruritis and rash (n=1)	2-12w	High risk of bias (Cochrane)
Mota et al 2017; Portugal; Case series	Finasteride 1 mg/d (n=2) → 2.5 mg/d (n=1) and 4 mg/d (n=2)	n=5 (4F, 1M), Ages=6-11 Hurley I (n=5) PFT: topical/oral abx, isotretinoin	Improved: 100% (5/5)	8, 12, 24w 5, 9mo	--
Randhawa et al 2013; Canada; Case series	Finasteride 5 mg/d → 10 mg/d (n=1)	n=3F, Ages=7, 15, 15 PFT: topical/oral abx, isotretinoin, OCPs; CT: ALA-PDL (n=1), topical abx (n=1), retinoids (n=1), OCPs (n=2), oral abx (n=3)	Improved: 100% (3/3)	2.5, 3, 6y	--
Spironolactone					
Collier et al 2020; US; Cross-sectional	Spirono-lactone	n=79F	Improved: 42.4% (28/66) Unchanged: 56.1% (37/66) Worsened: 1.5% (1/66)	Not reported	Poor quality Total: 5/10 Selection: 3/5 Comparability: 0/2 Outcome: 2/3
Golbari et al 2019; US; Retrospective cohort	Spironolac-tone 75 mg/d (average dose) n=10 increased dose n=2 reduced dose	n=46F, Mean age=35.1 ± 10.3 Hurley I (7%), II (74%), III (11%) PFT: abx, retinoids, biologics; CT: abx (37%), OCPs (30%), retinoid (2%), biologic (2%), steroid (2%)	Pain score: 2.7±2.4 → 1.2±1.6 (P=0.01) Lesions: 3.4±3.3 → 2.1±2.4 (P=0.02) HS-PGA: 2.6±0.9 → 2.0±1.0 (P<0.001) AE: nausea (7%), dizziness (4%), breast tenderness (2%), changes in urination (2%)	Mean f/u time: 7.1 mo (0.75-28 mo)	Poor quality Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Lee and Fischer 2015; Australia; Case series	Spironolac-tone 100 mg/d (n=18) → 125 mg/d (n=1) and 150 mg/d (n=1)	n=20F, Mean age=31.7 (14-59) HS-PGA: mild (n=5), moderate (n=12), severe (n=3) PFT: abx, antiviral, antifungal, excision, CAM, isotretinoin, OCPs; CT: abx (n=5), CPA (n=3), LNG (n=4)	HS-PGA: Complete response: 55% (11/20) Partial response: 30% (6/20) Unchanged: 15% (3/20) AE: altered mood and dizziness (n=1)	3 mo	--

TABLE 1. CONTINUED

Anti-Androgen Treatments for Hidradenitis Suppurativa					
Study reference	**Intervention**	**Patient characteristics**	**Treatment response and adverse effects**	**Response timepoint**	**Study quality^**
Spironolactone					
Kraft and Searles 2007; Canada; Retrospective cohort	Spironolactone 100 mg/d	n=3F, Of total number of pts in study: Mean age=33 (11-65) PFT: topical cleansers, topical/oral abx, drainage, excision	Improved: 33.3% (1/3) Unchanged or worsened: 66.7% (2/3) AE: menstrual irregularities (n=1), heart palpitations (n=1)	Treatment duration: 3-96 mo	Good quality Total: 8/9 Selection: 4/4 Comparability: 1/2 Outcome: 3/3
McPhie et al 2019; Canada; Retrospective cohort	Spironolactone 100 mg/d	n=12, Of total number of pts in study: Age=37.68 (18-88) CT: abx (n=1), ILK (n=1), isotretinoin (n=1), ADA (n=4)	IHS4: Improved: 41.7% (5/12) Unchanged: 50% (6/12) Worsened: 8.3% (1/12)	F/u 1-37 mo Mean tx duration: 15 mo +/- 10 mo	Poor quality Total: 7/9 Selection: 4/4 Comparability: 0/2 Outcome: 3/3
Peterson et al 2020; US; Retrospective cohort	OCPs or spironolactone	n=27	Improved: 81.5% (22/27) Unchanged: 18.5% (5/27)	Not reported	Poor quality Total: 7/9 Selection: 4/4 Comparability: 0/2 Outcome: 3/3
Quinlan et al 2020; Ireland; Retrospective cohort	Spironolactone 50 mg/d (n=4), 100 mg/d (n=22)	n=26F, Mean age=33 (20-56) Hurley I (n=4), II (n=20), III (n=2) PFT: abx, metformin, dapsone, liraglutide, ILK, surgery; CT: metformin (n=17)	Mean lesion count improved: 2 → 1 DLQI improved: 13 → 10 34.6% (9/26) had reduction of DLQI >5 7.7% (2/26) discontinued d/t AE AE: GI upset (n=2)	Mean duration of f/u: 6 mo (2-17 mo)	Poor quality Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Buserelin acetate, leuprolide, flutamide					
Bogers et al 1992; Netherland; Case report	Buserelin acetate 0.21 mg TID	n=1F, Age=30 PFT: topical/oral abx, isotretinoin, excision, OCPs, CPA, tamoxifen, progesterone; CT: estradiol valerate	Remission for 10 mo, including for 3 mo with concomitant estradiol valerate AE: mild vasomotor symptoms and other signs of estrogen deprivation	10 mo	--
Camisa et al 1989; US; Case report	Leuprolide 1 mg/d for 2 w → 0.5 mg/d for 10 w → 1 mg/d for 3 mo	n=1F, Age=33 PFT: oral abx; CT: oral/IV abx, isotretinoin, systemic steroid	Improvement in vulva and perineum AE: mild vasomotor symptoms	9 mo	--
Li et al 2018; China; Case report	Flutamide 250 mg/d →125 mg/d at 2 mo	n=1F, Age=39	2mo: improved 1y: Decreased frequency and severity of flares	1 y	--
Hormonal contraceptives					
Collier et al 2020; US; Cross-sectional	OCPs (n=166) Hormonal IUD (n=69) Medroxyprogesterone acetate (n=55) Birth control implant (n=29) Vaginal ring (n=13) Transdermal patch (n=5)	n=337F	IUD: Improved: 14.5% (8/55) Unchanged: 52.7% (29/55) Worsened: 32.7% (18/55) Birth control pill: Improved: 26.1% (31/119) Unchanged: 63% (75/119) Worsened: 10.9% (13/119) Birth control implant: Improved: 15.4% (4/23) Unchanged: 53.8% (14/23) Worsened: 19.2% (5/23) Transdermal patch: Improved: 50% (1/2) Unchanged: 50% (1/2) Depo-Provera: Improved: 8.8% (3/34) Unchanged: 50% (17/34) Worsened: 41.2% (14/34) Vaginal ring: Unchanged: 85.7% (6/7) Worsened: 14.3% (1/7)	Not reported	Poor quality Total: 5/10 Selection: 3/5 Comparability: 0/2 Outcome: 2/3
Hormonal contraceptives					
Peterson et al 2020; US; Retrospective cohort	OCPs or spironolactone	n=27	Improved: 81.5% (22/27) Unchanged: 18.5% (5/27)	Not reported	Poor quality Total: 7/9 Selection: 4/4 Comparability: 0/2 Outcome: 3/3

TABLE 1. CONTINUED

Anti-Androgen Treatments for Hidradenitis Suppurativa					
Study reference	**Intervention**	**Patient characteristics**	**Treatment response and adverse effects**	**Response timepoint**	**Study quality^**
Hormonal contraceptives					
Stellon and Wakeling 1989; UK; Case series	30 mg EE + 150 mg LNG (n=4); 30 mg EE + 150 mg LNG+ norethisterone (n=2); 2 mg ED + 0.03 mg EE, 30 mg EE + 150 mg LNG, 0.03 mg EE 0.15 mg LNG (n=1)	n=7F, Mean age=24.4 (17-39) PFT: abx, surgery	HS developed after 1 mo (n=2), 2 mo (n=3), 8 mo (n=1), 24 mo (n=1) 28.6 % (2/7) complete resolution with d/c of OCPs 42.9% (3/7) improved with change to higher estrogen: progestogen ratio OCP 14.3% (1/7) relapsed within 1mo of switching to 0.03 mg EE and 0.15 mg desogestrel from 30 mg EE and 150 mg LNG 14.3% (1/7) on progestogen-only pills continued to relapse	Onset of HS after OCP initiation: 2-24 mo	--
Cyproterone acetate					
Collier et al 2020; US; Cross-sectional	Cyproterone	n=5F	Unchanged: 80% (4/5) Worsened: 20% (1/5)	Not reported	Poor quality Total: 5/10 Selection: 3/5 Comparability: 0/2 Outcome: 2/3
Goldsmith and Dowd 1993; UK.; Case report	CPA 100 mg/d and EE 50 ug/d	n=1F, Age=18 PFT: abx, isotretinoin, antimalarials, drainage; CT: oral abx	3mo: scalp, face, follicular papules resolved; no new lesions 4mo: R axillary suppuration resolved 6mo: active disease resolved	6 mo	--
Kraft and Searles 2007; Canada; Retrospective cohort	Diane-35 daily Diane-35 + CPA 25 mg daily CPA 12.5 mg daily Spironolactone 100 mg/d CPA 25 mg + spironolactone 100 mg/d	n=26F, Of total number of pts in study: Mean age=33 (11-65) PFT: topical cleansers, topical/oral abx, drainage, excision	57.7% (15/26) improved within 1-6mo: Diane-35 daily (n=8) Diane-35 + CPA 25 mg daily (n=5) CPA 12.5 mg/d (n=1) CPA 25 mg + spironolactone 100 mg/d (n=1) 42.3% (11/26) had no improvement or worsening on Diane-35 alone, Diane-35 + CPA, CPA alone, CPA + spironolactone AE: Diane-35 + CPA: Menstrual irregularity (n=2), hair loss (n=1), mood changes (n=1), bloating (n=1), abdominal cramps (n=1), decreased libido (n=1)	Tx duration: 3-48 mo	Good quality Total: 8/9 Selection: 4/4 Comparability: 1/2 Outcome: 3/3
Cyproterone acetate					
Mortimer et al 1986; UK; Prospective trial	CPA 50 mg/d and EE 50 ug EE 50 ug/norgestrel 500 ug (E50) Crossover at 6mo	n=24F, Median age=27 (20-44) Moderate to severe	Complete response: 29.2% (7/24) Partial response: 20.8% (5/24) No response: 16.7% (4/24) 8.3% (2/24) deteriorated at 12mo 16.7% (4/24) withdrew d/t side effects 8.3% (2/24) withdrew d/t HS exacerbation No difference between 2 groups, E50 reduced testosterone more than CPA (P<0.05) AE: E50: "minor" side effects (n=8); CPA: Weight gain, headaches, breast soreness (n=5)	Crossover at 6 mo Response measured at 12 mo	Unclear risk of bias (Cochrane)
Sawers et al 1986; UK; Case series	CPA 100 mg/d and EE 50 ug EE reduced to 30 ug and CPA to 50 mg/d at various timepoints	n=4F, Ages=24, 29, 33, 39 PFT: abx, radiotherapy, surgery, OCPs	100% (4/4): rapid improvement maintained during therapy 75% (3/4): worsening of sx w/ CPA dose reduction to 50 mg/day 25% (1/4): recurrence during cycles when CPA not taken 50% (2/4): no recurrence after treatment was stopped at 5 mo (n=1) and 14 mo (n=1) 25% (1/4): recurrence after 6 mo AE: Depression (n=4), breast tenderness (n=1), amenorrhea (n=1 after treatment discontinuation)	Up to 14 mo	Good quality Total: 8/9 Selection: 4/4 Comparability: 1/2 Outcome: 3/3

Abbreviations: Abx, antibiotics; AE, adverse events; BID, two times a day; BP, benzoyl peroxide; CAM, complementary and alternative medicine; CPA, cyproterone acetate; CT, concomitant treatments; D, day; DLQI, Dermatology Life Quality Index; d/t, due to; ED, ethynodiol diacetate; EE, ethinyl estradiol; F, female; f/u, follow up; GI, gastrointestinal; HS-PGA, Hidradenitis Suppurativa-Physician Global Assessment; IFX, infliximab; IHS4, International Hidradenitis Suppurativa Severity Score System; ILK, intralesional kenalog; IUD, intrauterine device; IV, intravenous; L, left; LNG, levonorgestrel; m, male; mg, milligrams; MHT, masculinizing hormonal therapy; mo, month; n, number; OCP, oral contraceptive; PFT, previously failed treatments; pt, patient; R, right; SAPHO, Synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; sx, symptoms; TID, three times a day; tx, treatment; w, week; y, year

^Cochrane risk of bias used for clinical trials. Newcastle-Ottawa scale (NOS) used for case-control/cross-sectional/cohort studies. Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality - AHRQ - standards (good, fair, and poor):
Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain
Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain
Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome/Exposure domain

TABLE 2.

Metabolic Treatments for Hidradenitis Suppurativa

Study reference	Intervention	Patient characteristics	Treatment response and adverse effects	Response timepoint	Study quality^
Metformin					
Arun et al 2009; US; Case report	Metformin 500 mg/d → 1 g/d at 3 mo	n=1F, Age=50 PFT: oral abx	3 mo: reduced frequency and duration of flares 4 mo: no drainage from sinus and abscesses, reduced pain in axilla	3, 4 mo	--
Collier et al 2020; US; Cross-sectional	Metformin	n=84F	Improved: 18.8% (13/69) Unchanged: 73.9% (51/69) Worsened: 7.2% (5/69)	Not reported	Poor quality Total: 5/10 Selection: 3/5 Comparability: 0/2 Outcome: 2/3
Fania et al 2020; Italy; Case report	Metformin 1 g/d	n=1M, Age=22 SAPHO PFT: oral abx, drainage; CT: ADA, MTX, systemic steroid, ILK	Continued flares on metformin, improved after ILK Radical surgery of armpit lesions after 3mo; no lesions in axilla 5mo after surgery	Not reported	--
Jennings et al 2020; Ireland; Retrospective cohort	Metformin Mean daily dose: 1.5 g/d (500 mg-3 g)	n=53 (45F, 8 M), Mean age=37 (19-62) Hurley I (n=2), II (n=38), III (n=13) CT: oral abx (n=2), dapsone (n=7), acitretin (n=1), ADA (n=1)	Physician assessment: Complete response: 13.2% (7/53), all Hurley II Partial response: 54.7% (29/53) No response: 24.5% (13/53) AE: GI distress (n=6)	At least 3 mo follow up and 1 mo treatment, Mean tx duration: 11.3 mo (1-36)	Poor quality Total: 6/9 Selection: 3/4 Comparability: 0/2 Outcome: 3/3
Kraft and Searles 2007; Canada; Retrospective cohort	Metformin 500 mg BID	n=1F, Of total number of pts in study: Mean age=33 (11-65) PFT: topical cleansers, topical/oral abx, drainage, excision	No improvement	6 mo	Good quality Total: 8/9 Selection: 4/4 Comparability: 1/2 Outcome: 3/3
McPhie et al 2019; Canada; Retrospective cohort	Metformin 500 mg/d (n=1) 500 mg BID (n=3)	n=4, Of total number of pts in study: Mean age=37.68 (18-88) CT: oral abx (n=1), isotretinoin (n=1)	Metformin 500 mg/d: Change in IHS4 score: -1 Metformin 500 mg BID: Average change in IHS4 score: +2 (for pts with mild IHS4 score at start), -6 (for pts with moderate IHS4 score)	F/u: 1-37 mo Mean tx duration: 15.29 mo	Poor quality Total: 7/9 Selection: 4/4 Comparability: 0/2 Outcome: 3/3
Moussa et al 2020 ; US; Retrospective cohort	Metformin 500 mg/d → 500 mg BID after 1w	n=16 (12F, 4M), Mean age=13.7 ± 3 Hurley I (n=11), II (n=5)	Improved: 31.3% (5/16) No response: 31.3% (5/16) Lost to follow up or no data available: 37.5% (6/16) AE: GI distress (n=1), mood changes (n=1)	Not reported	Poor quality Total: 5/9 Selection: 3/4 Comparability: 0/2 Outcome: 2/3
Verdolini et al 2013; UK; Prospective trial	Metformin 500 mg/d → 500 mg BID (n=9), 500 mg TID (n=15), 850 mg BID (n=1)	n=25 (22F, 3M), Age=17-51 PFT: abx, isotretinoin, acitretin	Sartorius: Improved: 72% (18/25) (7 had >50% improvement) No response: 28% (7/25) Improved DLQI (15 ± 4.96 → 7.65 ± 7.12), decreased number of workdays lost, improved depression (n=11 → n=7) AE: minor GI disturbances	0, 12, 24 w	High risk of bias (Cochrane)
Liraglutide					
Jennings et al 2017; Ireland; Case report	Liraglutide 0.6 mg/d → 1.8 mg/d	n=1F, Age=31 HS-PGA: severe PFT: oral abx, spironolactone, metformin, ADA, etanercept, dapsone	4w: HS-PGA/DLQI improved, weight decreased by 4.5 kg, reduced analgesia requirement 8w: weight decreased by 6.5 kg total, HS well controlled	4, 8 w	--
Khandalavala et al 2017; US; Case report	Liraglutide 0.6 mg/d → 1.8 mg over 2 mo	n=1F, Age=19 PFT: oral/IV abx, isotretinoin, OCPs, surgery, finasteride; CT: dapsone, LNG-EE, metformin, finasteride	Lost 40 lbs over 6 mo 3 mo: new lesions resolved faster 6 mo: less intense and frequent flares At unspecified time, large perianal abscess developed; required surgery 3 y: significant healing, no new lesions for 6mo	3, 6, 15 mo, 3 y	--

Abbreviations: Abx, antibiotics; ADA, adalimumab; AE: adverse events; BID, two times a day; BP, benzoyl peroxide; CR, complete response; CT, concomitant treatments; D, day; DLQI, Dermatology Life Quality Index; d/t, due to; EE, ethinyl estradiol; F, female; f/u, follow up; g, gram; GI, gastrointestinal; HS-PGA, Hidradenitis Suppurativa-Physician Global Assessment; IHS4, International Hidradenitis Suppurativa Severity Score System; ILK, intralesional kenalog; IUD, intrauterine device; IV, intravenous; L, left; lbs, pounds; LNG, levonorgestrel; m, male; mg, milligrams; mo, month; MTX, methotrexate; n, number; OCP, oral contraceptive; PFT, previously failed treatments; pt, patient; R, right; SAPHO, Synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; sx, symptoms; TID, three times a day; tx, treatment; w, week; y, year

^Cochrane risk of bias used for clinical trials. Newcastle-Ottawa scale (NOS) used for case-control/cross-sectional/cohort studies. Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality - AHRQ - standards (good, fair, and poor):
Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain
Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome/Exposure domain
Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome/Exposure domain

study that grouped the effects of OCPs and spironolactone on HS for an overall response rate of 81.5% (22/27).[27]

Cyproterone Acetate

Over half (53.3%, 32/60) of patients across studies exhibited a response to cyproterone acetate, progesterone with anti-androgenic properties, and ethinyl estradiol mono/combination therapy. In 1986, Mortimer et al enrolled 24 women in a prospective cross-over trial comparing regimens of cyproterone acetate (CPA) 50 mg/ethinyl estradiol 50 ug with ethinyl estradiol 50 ug/norgestrel 50 ug (E50). Treatments were given on days 5 to 25 of the menstrual cycle; cross-over occurred at month 6. After 12 months, 29.2% of patients had complete resolution of disease while 20.8% of patients had a partial response. Notably, 16.6% of patients withdrew from this study due to adverse effects and 8.3% dropped out due to deterioration of disease.[28]

Similarly, Sawers et al described 4 patients on CPA 100 mg/day for 10 days followed by ethinyl estradiol 50 ug/day for 21 days in repeated cycles; all patients experienced rapid improvement in their symptoms.[29] A case report by Goldsmith and Dowd also demonstrated that the combination of CPA and ethinyl estradiol resulted in resolution of active disease after 6 months.[30] Kraft and Searles compared the efficacy of CPA, ethinyl estradiol, and spironolactone either as monotherapy or in various combinations. Amongst 26 patients, 57.7% exhibited a response after 1 to 6 months.[22] On the contrary, in Collier et al's cross-sectional survey study, 0% (0/5) of patients reported that CPA improved their symptoms.[3]

Side effects including weight gain, headaches, and breast soreness were reported with both CPA monotherapy and combination therapy with ethinyl estradiol. Depression, mood changes, amenorrhea, menstrual irregularity, hair loss, bloating, abdominal cramps, and decreased libido were also noted among patients.[22,28,29]

Testosterone

Two studies discussed worsening HS symptoms with testosterone therapy in transgender men. Buonomo et al reported a case series of two transgender patients who developed HS exacerbations after initiating testosterone therapy. Both of the patients had a resolution of flares after the testosterone dose was decreased and one of the patients responded to concurrent finasteride therapy.[12] Another case study described a 25 year old transgender patient whose lesions worsened while on testosterone therapy.[31] On the contrary, a 1952 study by Cornbleet described 8 HS patients on testosterone propionate who improved to have stable or quiescent disease. However, concomitant penicillin was used in 4 of the patients and the time frame for treatment and follow-up was unclear.[32]

Metabolic Treatments

Metformin

Metformin therapy was effective in 46.0% (74/161) of patients across studies with metformin in HS.[3,22,33-35] In the studies which reported disease severity, 13 patients had Hurley stage I disease, 43 patients stage II, and 13 patients stage III. Verdolini et al enrolled 25 patients in a prospective trial and reported a response in 72% of patients on various doses of metformin after 24 weeks.[33] In 2020, a retrospective cohort study by Jennings et al discussed the effects of metformin in 53 patients; 13 patients were obese and 10 patients had type 2 diabetes mellitus (T2DM). On an average dose of 1.5 g daily, 13.2% of patients had complete remission and 54.7% had a partial response. However, 20.8% of patients required an additional agent due to persistent symptoms.[34] Moussa et al found that in 16 patients with HS, 31.3% improved on metformin; however, 37.5% of patients were lost to follow-up.[35]

A retrospective study of patients by McPhie et al found that one patient on 500 mg daily of metformin had improvement in their IHS4 score. Of 3 patients who were on 500 mg twice a day, those with a mild IHS4 had worsening of their score (mean +2) but those with a moderate IHS4 had improvement (mean -6).[18] Kraft and Searles included one patient on metformin 500 mg twice daily in their retrospective study but the patient did not show any improvement at 6 months.[22] Arun and Loffeld reported a case of a patient with T2DM on metformin 500 mg daily which was increased to 1 g daily at month 3. The regimen resulted in reduced frequency and duration of flares, resolution of drainage from sinuses and abscesses, and reduced pain after 4 months.[36] Conversely, Fania et al discussed one patient with SAPHO syndrome who was placed on metformin 1 g daily but continued to have HS flares. The flares improved after intralesional steroid injections and the patient ultimately had to receive surgery for an axillary flare after 3 months.[37] In a 2020 cross-sectional survey study, 18.8% (13/69) of patients reported an improvement in metformin therapy.[3] Across all studies, metformin was generally well tolerated although mood changes and minor GI disturbances were reported in some patients.[33–35]

Liraglutide

Two case reports discussed the effects of liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, on HS symptoms. One patient was started on 0.6 mg of liraglutide which was titrated to 1.8 mg daily due to extensive disease. After 4 weeks of treatment, she had mild residual disease and her DLQI improved from 24 to 14; she lost approximately 14 pounds after 8 weeks.[38] Another patient, who took liraglutide concurrently with metformin and finasteride, lost 40 pounds over 6 months and had less intense and frequent HS flares. Significant healing was noted after 3 years.[39] No adverse events were reported.

DISCUSSION

This systematic review of 30 studies found that hormonal therapies appear effective and safe in certain patients; although the patient populations which would benefit the most from these treatments have not yet been defined. Currently, the literature supports the use of spironolactone (in females), finasteride, and metformin, with the response rates for these interventions being over 40%. More data are needed to understand which types of contraceptives would be most helpful for patients with HS. Furthermore, only 10% of included studies were prospective trials.

Spironolactone has been the most extensively studied anti-androgen treatment (186 patients) to date and has been shown to improve outcomes such as pain, lesion counts, and HS-PGA scores. The optimal dosing of spironolactone is unclear. Golbari et al found that there was no difference in improvement between patients who received less than 75 mg of spironolactone daily and those who received more than 100 mg daily; however, data on Hurley stage, BMI, and comorbidities for patients who received higher doses vs lower doses were not available. Finasteride has been shown to induce remission for many years and re-introduction of the drug was successful in suppressing recurrences in some patients; data comparing efficacy of finasteride vs spironolactone for HS in women are lacking.

More than half of patients on CPA, an anti-androgenic progesterone that is often taken in combination with estrogen as a combined birth control pill, reported a response. However, certain types of contraceptives such as IUDs or oral contraceptives with high levels of progesterone may exacerbate HS. The precise mechanism by which androgens, estrogen, and progesterone influence the HS disease course is unclear; but studies have shown that androgen levels (testosterone and dehydroepiandrosterone sulfate) in HS patients are normal.[40,41] Differences in sensitivity to androgens and in situ conversion of normal androgens to more potent androgens in sebaceous glands may play a role in HS exacerbations.[42,43] Two studies describing HS exacerbations with testosterone therapy in transgender individuals support the role of androgens in HS exacerbations.[12,31] HS also has a known association with metabolic syndrome which causes increased insulin and insulin-like growth factor 1 (IGF-1) levels; both of these hormones result in prolonged binding between androgens and their receptors which may lead to increased keratinization in hair follicles and subsequent obstruction and inflammation.[44,45] Similar to androgens, progesterone may induce hyperkeratinization and elevated insulin levels which may contribute to HS flares.[46–48] The potential synergistic benefit of an OCP combined with spironolactone and the effect of an anti-androgenic progesterone alone (eg, drospirenone-only contraceptive)[49] on HS symptoms are also understudied. Furthermore, investigation into whether the presence of menstrual HS flares predicts response to anti-androgenic therapy is warranted.

Metabolic treatments also showed benefits in reducing the HS disease burden. Beneficial effects of metformin in HS may be due to its anti-inflammatory properties.[50,51] Metformin may also desensitize androgen receptors by decreasing peripheral insulin levels and minimize de novo production of androgens from ovaries.[52,53] While liraglutide has only been studied in two patients, both reported marked weight loss and significant clinical improvement in HS.

Study limitations, common to most systematic reviews on HS treatments, include the small number of prospective studies and small sample sizes in studies. All but two studies took place in North America and Europe, which limits the generalizability of our findings. In addition, there was heterogeneity amongst the studies with regard to variables used to assess outcomes and timepoints of efficacy measurement. Specific patient characteristics, such as presence of peri-menstrual flares or comorbid PCOS, may help predict response to hormonal treatments; but we were unable to separate the response rate for these patients from the overall efficacy data.

Overall, hormonal therapies are promising treatment options for patients with HS. Mechanistic studies are warranted to examine the role of sex hormones and insulin in HS pathophysiology. Large randomized controlled trials are needed to explore the efficacy, safety, and optimal dosing of hormonal treatments in HS and identify sub-populations that may benefit the most.

DISCLOSURES

JLH is on the Board of Directors for the Hidradenitis Suppurativa Foundation, has served as a consultant for Boehringer Ingelheim, Novartis, and UCB, and has served as a consultant and speaker for AbbVie. VYS is on the board of directors for the Hidradenitis Suppurativa Foundation (HSF), is a stock shareholder of Learn Health and has served as an advisory board member, investigator, speaker, and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Incyte, Boehringer-Ingelheim, Alumis, Aristea Therapeutics, Menlo Therapeutics, Dermira, Burt's Bees, Galderma, Kiniksa, UCB, WebMD, TARGET-Pharmasolutions, Altus Lab, MYOR, Polyfin, GpSkin, and Skin Actives Scientific. All other authors report no conflicts of interest.

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ORIGINAL ARTICLE

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Off-Label Use of Baricitinib in Dermatology

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ABSTRACT

The current US Food and Drug Administration (FDA) indications for baricitinib include alopecia areata, rheumatoid arthritis, and COVID-19. However, increasing evidence indicates that baricitinib is effective in treating a variety of dermatological conditions. This review article comprehensively presents the available literature on this topic and will be of interest to practitioners in the field.

These disorders may be broadly classified as connective tissue diseases, eczematous dermatoses, alopecias, vascular disorders, granulomatous diseases, neutrophilic dermatoses, vitiligo, psoriasis, lichenoid disorders, and other miscellaneous disorders.

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INTRODUCTION

Baricitinib is a reversible Janus kinase (JAK) 1 and 2 inhibitor approved for use in the European Union and the United States for various dermatological conditions. In the US, current US Food and Drug Administration (FDA) indications for baricitinib include alopecia areata (AA), rheumatoid arthritis (RA), and COVID-19. Despite this, baricitinib has also been used as an off-label treatment for other conditions when other treatment options may have failed or proved inefficacious.

JAK inhibition is a therapeutic strategy for immune and inflammatory diseases through mediating the JAK-STAT pathway.[1] Since cytokines that depend on JAK are important factors in immunopathology, JAK inhibitors seek to prevent proinflammatory downstream signaling. Baricitinib is a reversible JAK1/JAK2 inhibitor that was first approved in the European Union in February 2017. Other JAK inhibitors differ in target selectivity and downstream effects. For example, ruxolitinib, which was the first approved JAK inhibitor, targets JAK1/JAK2 and has been used in the treatment of psoriasis and AA.[1] Tofacitinib, which is used to treat rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis, is a potent inhibitor of JAK3 and also inhibits JAK1, but is less selective for JAK2.[2] Lastly, upadacitinib, which is used to treat active RA, is a JAK1 inhibitor and inhibitor of IL-3, GM-CSF, and G-CSF.[2]

Conditions in which baricitinib has been used may be broadly categorized into connective tissue diseases, eczematous dermatoses, alopecias, vascular disorders, granulomatous diseases, neutrophilic dermatoses, vitiligo, psoriasis, lichenoid disorders, and other miscellaneous disorders. Herein, we review potential off-label uses of baricitinib.

MATERIALS AND METHODS

The Pubmed/MEDLINE database was queried with the search 'baricitinib OR 'Olumiant' OR 'LY3009104' OR 'INCB028050'. The US National Library of Medicine (ClinicalTrials.gov) database was queried with the terms 'baricitinib', 'Olumiant', 'LY3009104', and 'INCB028050'. After removing duplicate articles, remaining studies were screened by title and abstract for off-label uses of baricitinib in dermatology. Full text screening was then conducted to identify articles that described clinical outcomes for patients using baricitinib for dermatologic conditions. The only dermatology-related FDA indication for baricitinib is AA. The other indications are for COVID-19 hospitalized patients and RA. Non-English articles and articles that described on-label use were not included. No time restrictions were applied and searches were performed in July 2022. As atopic dermatitis (AD) has been approved for use in the European Medicine Agency (EMA), non-randomized control trial studies of baricitinib treatment for AD, including case reports and retrospective studies, will not be covered here; but they are referenced for reviewing below.

Connective Tissue Diseases

Systemic lupus erythematosus

Type 1 and Type 2 interferons that are present in systemic lupus erythematosus (SLE) depend on the JAK/STAT pathway.[3] Moreover, literature indicates that inhibiting this JAK/STAT pathway plays an important role in reducing SLE inflammation.[4] The literature documents reports of using baricitinib to treat chilblain lupus, cutaneous lupus erythematosus, and refractory systemic lupus erythematosus.

The strongest evidence comes from a double-blind, randomized, placebo-controlled, phase 2 trial in patients (n=314) with SLE.[5-6]

TABLE 1.

Randomized Controlled Trial Data and Other Prospective Data on Baricitinib for Off-Label Indications Beyond Atopic Dermatitis

Disease	Study Type (number of patients on baricitinib)	Efficacy	Treatment Duration (dose)	Citation
Systemic lupus erythematosus (SLE)	RCT (n=209)	70 (67%) of 104 patients receiving baricitinib 4 mg (odds ratio [OR] vs placebo 1·8, 95% CI 1·0–3·3; *P*=0·0414) and 61 (58%) of 105 patients receiving baricitinib 2 mg (OR 1·3, 0·7–2·3; *P*=0·39) achieve resolution week 24, resolution of SLE Disease Activity Index-2000 arthritis or rash at 24 weeks.	24 weeks (2 mg or 4 mg) Dose 1: 2 mg n=105, Dose 2: 4 mg n=104)	(5)
Juvenile dermatomyositis (JDM)	Expanded Access (n=4)	Significant improvement in clinical scores from week 4 (Physicians Global Assessment, Pt Global activity, CDASI activity score)	24 weeks	(18)
Giant Cell Arteritis	Open-label trial (n=15 enrolled; 14 completed all 52 weeks; 1 discontinued)	Only 1 of 14 (7%) patients relapsed during the study.	52 weeks (4 mg) and varying doses of prednisone	(57)
Psoriasis	RCT Dose-Ranging (n=271 randomized, 237 received)	More North American patients in the 8 mg (43%) and 10 mg (54%) baricitinib groups than in placebo group (17%; *P*<0.05) achieved PASI-75 at week 12. All baricitinib groups except 2 mg had statistically significantly greater mean changes from baseline in their PASI scores at week 12 and had higher rates of PASI-50 compared with placebo. PASI-90 responses in the 8 mg and 10 mg groups at weeks 8 and 12 were statistically significant. More than 81% of PASI-75 responders-maintained scores through week 24.	Part A week 12, Part B week 12 (2/4/8/10 mg)	(78)

The 4 mg baricitinib dose, as opposed to the 2 mg dose, significantly improved the signs and symptoms of SLE in patients who previously received standard care but who had not improved. Anti-dsDNA antibody levels of patients from this trial were analyzed.7 Baricitinib 2 mg and 4 mg significantly decreased median anti-dsDNA levels as compared with placebo in patients with elevated anti-dsDNA at baseline.

Several case reports and series offer evidence for the use of baricitinib in the treatment of SLE. A case series of 3 patients with familial chilblain lupus who were treated with 4 mg per day baricitinib for 3 months reported all patients experiencing significant improvement of cutaneous lupus lesions along with inhibition of systemic type I interferons.[8] A case has been reported of baricitinib for recalcitrant subacute cutaneous lupus erythematosus (SCLE) with concomitant frontal fibrosing alopecia (FFA).[9] The patient received baricitinib 4 mg for 2 months with full clearance of SCLE and halted progression of the FFA. Low-dose baricitinib was efficacious in the treatment of patchy alopecia and sicca syndrome as reported in the case of an SLE patient.[10] The patient was treated with baricitinib 2 mg per day, with PSL 10 mg per day, and HCQ. Significant hair regrowth was observed after 1.5 months of treatment and her European Alliance of Associations for Rheumatology Sicca Score improved from 6 to 2. After 3 months, no alopecia or sicca syndrome was observed.

Barcitinib has been used in the refractory setting for SLE as reported in 2 cases.[11] The first case reports baricitinib as being efficacious for the treatment of refractory papulosquamous eruption in a patient with systemic lupus erythematosus. After 4 weeks of baricitinib 4 mg per day, there was nearly complete resolution of relevant skin lesions. The second case had a history of SLE with refractory skin manifestations to topical corticosteroids.[12] Treatment with 4 mg per day baricitinib resulted in rapid decline in skin manifestations. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was improved at a value of 3 at 6 months down from 21 at baseline. A patient with non-scarring alopecia and previous history of SLE experienced stop of hair loss and prominent hair growth by the 8th week of treatment with 4 mg per day baricitinib.[13]

Dermatomyositis

Given the elevated Type 1 interferon signaling in dermatomyositis (DM), JAK inhibition may be useful in disease management.[14] JAK inhibitors that have been used in patients with DM include tofacitinib and ruxolitinib.[15,16]

There are no randomized controlled trials (RCTs) testing baricitinib in patients with DM, but there is evidence in cases. One case documents a 25-year-old female patient with anti-MDA5 antibody-positive dermatomyositis and AA.[17] Previous treatments did not completely relieve symptoms. Two mg daily

baricitinib was used along with prednisone and tacrolimus. Five months after treatment, the patient's rash was significantly relieved, and hairs grew in areas of alopecia with normal distribution density, thickness, and color.

A case series of 4 patients documents the use of baricitinib in refractory juvenile dermatomyositis (JDM).[18] These 4 patients had chronically active JDM and previously failed 3 to 6 immunomodulatory medications and thus were enrolled in a compassionate use study.[19] Significant improvements were seen in Physician Global Activity, Patient Global Activity, Extramuscular Global Activity, and Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI).

Another case documents a pediatric patient with JDM who responded positively to treatment with baricitinib.[20] In another case series (n=3 patients) each patient had a positive response to baricitinib.[21] Baricitinib improved lesions after 4 weeks of treatment based on the Cutaneous Dermatomyositis Area and Severity Index (CDASI) version 2, and the Dermatology Life Quality Index (DLQI).

Systemic Sclerosis

IL-6 is elevated in systemic sclerosis and is associated with disease activity [22]. JAK inhibition may play a role in management of SS by inhibiting downstream signaling.[23] Several studies have investigated the use of baricitinib in patients with systemic sclerosis (SS). The first was an open label trial of 10 patients with diffuse cutaneous systemic sclerosis (dcSSc).[24] Skin thickening was significantly decreased and mRSS significantly improved at weeks 12 and 14 from baseline.

Case series and reports have also shown promise. There was improvement in articular symptoms in a patient with systemic sclerosis-RA overlap syndrome (SSc-RA) who had failed prednisone, methotrexate, abatacept and rituximab, and intravenous tocilizumab (TCZ-IV).[25] Another patient with RA and SS with Interstitial Pneumonia and Type 1 Diabetes (T1D) was effectively treated with baricitinib, methotrexate, and prednisolone.[26] Anti-citrullinated protein antibody levels decreased, and levels of CRP/ESR, RF, MMP-3, and SAA were normalized. She also had improvement in modified Rodnan total skin thickness (m-Rodman TSS) score.

Sjogren's Syndrome

Inhibition of JAK may be useful in treating Sjogren's syndrome through inhibiting the JAK/STAT signaling pathway resulting from activation of the type I interferon pathway.[27] A pilot study of patients diagnosed with Sjogren's syndrome found that baricitinib was well tolerated and improved symptoms of arthritis and skin manifestations.[28] EULAR primary Sjogren's syndrome Disease Activity Index (ESSDAI) scores, EULAR primary Sjogren's syndrome Patient Reported Index (ESSPRI), and Physician Global Assessment (PGA) scores all significantly decreased from baseline.

Eczematous Disorders

JAK/STAT signaling plays an important role in the pathophysiology of eczematous disorders. For example, JAK1 is critical in the expression of proinflammatory cytokines in AD such as IL-4, IL-5, IL-13, and IL-31.[29] Abrocitinib and upadacitinib have been used to treat AD.[30,31]

Atopic dermatitis

In Europe, baricitinib has been approved for use in patients with moderate to severe AD. However, the FDA has yet to approve baricitinib to treat AD in the US. The evidence for use of baricitinib is greatest in AD compared with the other off-label uses presented in this study. Whereas the other studies are mostly case reports, several clinical trials are testing the efficacy and safety of baricitinib.[32-39] The clinical trials of baricitinib for the treatment of AD have been extensively reviewed elsewhere.[40] In sum, baricitinib is efficacious in phase II and phase III RCTs in patients with moderate-to-severe AD. To be concise, other studies of baricitinib treatment for AD, including case reports, retrospective studies, will not be discussed but are referenced for review here.[41-45]

Hand eczema

A study of 2 case reports documents the treatment of chronic hand eczema (CHE) with baricitinib.[46] Both patients were treated with 4 mg daily baricitinib. After 16 weeks of treatment, Case 1's severe CHE was improved to "almost clear" with Hand Eczema Severity Index (HECSI) score of 4 down from 55 with Quality of Life in Hand Eczema Questionnaire (QOLHEQ) scores improved. Case 2's CHE was improved to "almost clear," with HECSI score of 8 down from 47 with QOLHEF improved.

Nodular prurigo

Several case reports document the use of baricitinib to treat nodular prurigo (NP). In the first case, the patient initially reported a 10/10 maximal intensity (numerical rating scale [NRS]) of itch with a diminished dermatological life quality index. This reduced to 2/10 to 3/10 at 3 months with eczematous and pruriginous lesions improved.[47] In another case of NP, the patient had a baseline Eczema Area and Severity Index (EASI) of 56.4 and itch numeric rating scale (NRS) of 6.[48] Upon treatment with 4 mg daily of baricitinib and emollients, pruritus and skin lesions improved rapidly (EASI50 reached at week 8). A separate case of methotrexate intolerant non-atopic PN was effectively treated with 4 mg daily baricitinib.[49] The pruritus improved in 1 week with peak NRS decreasing from 9 to 4, and effects continued through a 4-month treatment with few nodules left on the extensor arms.

Refractory Pruritus

There is one reported case of chronic pruritus of unknown origin refractory to dupilumab treated with baricitinib.[50] The patient presented with severe chronic pruritus and was started on 2 mg per day baricitinib following previous unsuccessful treatments. On day 5 the patient reported a 1/10 maximal intensity NRS. The patient self-discontinued treatment after 2 weeks of 1/10 NRS. The relief persisted beyond a visit 2 weeks later and improved a month later with 0/10 NRS at 3-month follow up.

Alopecias

Promotion of IL-15 production through JAK/STAT signaling has been implicated in alopecia.[51] IL-15 also stimulates IFN-g through JAK1/3 signaling.[51] JAK inhibitors including tofacitinib and ruxolitinib have been shown to improve symptoms in patients with alopecia.[51] While one of the indications of baricitinib in the US is AA, it has been used off-label to treat other hair conditions such as folliculitis decalvans (FD) and lichen planopilaris (LPP).

Folliculitis decalvans

A case series reported a reduction in symptoms, reduction in inflammation, and reduction in pustules in individuals with FD receiving baricitinib.[52]

Lichen planopilaris

A retrospective study of patients with LPP found an overall reduction in the median Lichen Planopilaris Activity Index (LPPAI) scores at the initial and latest reviews, (1.2; 20% P=0.021) and (1.3; 23.1% P=0.063), respectively.[53]

Vascular Disorders

Overactive JAK/STAT signaling is implicated in sustaining vascular inflammation and thrombosis.[54] Due to this, JAK is a potential therapeutic target in treating vascular disorders such as livedoid vasculopathy (LV) and giant cell arteritis (GCA).

Livedoid vasculopathy

In the case series literature, livedoid vasculopathy (LV) has been effectively treated with baricitinib.[55] Patients were resistant to conventional therapy but improved with baricitinib treatment.[55] Another case describes a patient with LV successfully treated with 4 mg per day baricitinib. All the lesions disappeared at the 3rd month following treatment.[56]

Giant cell arteritis

Evidence for the use of baricitinib includes a large study and case literature. The largest study of baricitinib in relapsing GCA is a prospective 52-week open-label study of 15 patients receiving 4 mg per day with a tiered glucocorticoid (GC) entry.[57-58] Treatment with baricitinib at 4 mg per day was well tolerated and showed preliminary efficacy in patients with relapsing GCA. A case report also indicates the successful treatment of relapsing GCA with off-label use of baricitinib in a 76 year old.[59] The patient was symptom free at month 6 following treatment with 4 mg per day of baricitinib and 20 mg per day of prednisone.

Granulomatous Diseases

IFN-g, a cytokine critical in granuloma formation, is used by the JAK/STAT signaling pathway.[60] Ruxolitinib has been used to treat refractory cutaneous sarcoidosis with improvement.[61] Treatment with off-labeled baricitinib has been reported in case studies of granulomatous diseases, including granuloma annulare (GA) and palisaded neutrophilic granulomatous dermatitis (PNGD).

Granuloma annulare

In the case of GA, the patient was treated with baricitinib 4 mg/day. Lesions started dissipating after 2 months and were almost cleared after 5 months with no relapse 4 months after withdrawal from baricitinib.[62]

Palisaded neutrophilic granulomatous dermatitis

In a separate case of PNGD, the patient's subcutaneous nodules became smaller and reduced in number, along with ease of treatment-resistant joint pain within 5 months of 4 mg daily baricitinib treatment.[63]

Neutrophilic Dermatoses

JAK inhibition has also been postulated to be effective in treating neutrophilic dermatoses, including pyoderma gangrenosum (PG) and Sweet syndrome (SS). A proposed pathomechanism of PG is that it occurs due to direct activation of JAK along with STAT.[64] It has also been hypothesized that there is over-regulation of the JAK/STAT in SS.[65] Tofacitinib has been used to treat PG[66] and ruxolitinib has been used to treat SS.[67] Thus, baricitinib is another proposed treatment.

Pyoderma gangrenosum

One study reports 2 cases of PG treated with 4 mg daily baricitinib.[68] Case 1 experienced no new lesions after 7 days and complete regression after 5 weeks. Case 2 had an outbreak of PG on the right leg, with lesions healing in 3 months.

Sweet syndrome

A separate case report describes the successful treatment of refractory RA-associated SS with baricitinib.[69] Their cutaneous eruption significantly improved at week 4 follow up after using oral baricitinib 2 mg daily. After 10 months on baricitinib, long-lasting remission of cutaneous and joint disease with no reported adverse effects was observed.

Vitiligo

IFN-γ–signaling and production of IFN-γ–dependent chemokines CXCL9, 10, and 11 are important in vitiligo pathogenesis.[70] Downregulating IFN-γ–signaling through JAK inhibition is thus seen as a potential therapeutic target for treating vitiligo.[71] Other

JAK inhibitors including ruxolitinib (JAK1/JAK2 targeting) and tofacitinib have been used to treat vitiligo.[72,73]

In one study, (n=4) patients with non-segmental progressing vitiligo were treated with oral baricitinib 4 mg daily during the first 4 weeks, followed by 2 mg daily through week 12.[74] All 4 patients achieved favorable clinical results at the end of week 12, with vitiligo area scoring index (VASI) scores significantly reduced, with re-pigmentation rates of 59.26 to 74.17%. Repigmentation of vitiligo has been reported in a case of a 67-year-old man with comorbid RA previously unsuccessfully treated with tofacitinib.[75] Baricitinib 4 mg per day was commenced with almost complete repigmentation of the hands and forearms observed with no adverse effects at month 8 follow up.

Psoriasis

JAK inhibition has been used in psoriasis through blocking the production of proinflammatory cytokines stemming from the IL-23/Th17 axis.[76] For example, tofacitinib, which is known to block JAK3, JAK2, and JAK1, has been used to treat patients with psoriasis.[77]

The highest evidence study for use of baricitinib in psoriasis was a dose-ranging, phase 2b double-blind RCT of baricitinib in patients (n=271) with moderate-to-severe plaque psoriasis.[78-79] This trial demonstrated that individuals with moderate-to-severe psoriasis treated with baricitinib for 12 weeks exhibited marked reduction in PASI scores; baricitinib was well tolerated over the 24-week trial period.

Other than the RCT, there has been a reported case of the successful treatment of psoriasis with baricitinib. There is one report of a 28-year-old female patient with acrodermatitis continua of Hallopeau (ACH), a variant of pustular psoriasis, whose pustules and joint swelling worsened despite previous treatment.[80] Treatment with baricitinib 2 mg per day improved pustular eruptions and joint swelling 5 days after treatment. Remission of the individual's fingernail pustules was maintained 5 months post treatment.

An adverse effect of baricitinib was reported in a 68-year-old woman with RA.[81] The patient was treated with baricitinib after previous unsuccessful treatment. Three weeks following baricitinib treatment, psoriasiform skin eruption on the scalp and upper limbs developed. As baricitinib did not ameliorate the RA, it was stopped; and, 2 months after topical steroids, the psoriasis resolved.

Lichenoid Disorders

JAK inhibition has been proposed as a therapeutic option in patients with lichenoid disorders as it may inhibit the downstream signaling of the IFN-g/CXCL10 axis that is responsible for persistent inflammation in patients with lichen planus and relies on the JAK-STAT pathway.[82] Several cases provide evidence for use of baricitinib in lichenoid disorders (lichen planus [LP] and lichen sclerosus [LS]).

Lichen planus

A woman in her 60s with severe nail lichen planus (NLP) was effectively treated with baricitinib.[83] After 2 months with baricitinib 4 mg daily, the appearance of the patient's nails substantially improved. The patient's nails were completely clear 4 months later. After reducing the dose to 2 mg, a minimal distal onycholysis on 1 finger (compatible with a small recurrence) was observed; however, the patient continued with treatment.

Another woman in her 60s presenting with chronic AA and coincidental oral LP (OLP) was effectively treated with 3.4 mg twice daily baricitinib after previous efficacious treatments.[84] Alongside regrowth hair regrowth, improvement of the patient's OLP was noted on examination after month 1 and was sustained after month 4. The patient reported almost complete resolution of oral irritation and discomfort.

Lichen sclerosus

A 2-year-old patient with LS who failed with 1% topical pimecrolimus cream observed repigmentation and improvement in tightness of skin after 2 months of 2 mg daily baricitinib treatment. Nearly half of the lesions were repigmented 6 months later.[85] A 21-year-old female diagnosed with LS was treated with 2mg daily baricitinib and photochemotherapy (PUVA) twice weekly after previous inefficacious treatments.[86] The skin lesions gradually repigmented and became elastic (3 months after treatment), and the patient indicated improvement in symptoms and quality of life through a validated LS questionnaire.

Miscellaneous

Aside from the conditions mentioned above, baricitinib has also been used to treat other dermatological conditions as reported in case reports. These include: cutaneous Kaposi's sarcoma,[87] Darier's disease,[88] epidermolysis bullosa pruriginosa,[89] graft vs host disease,[90] hypereosinophilic syndrome,[91] nodular histiocytosis,[92] refractory eosinophilic fasciitis,[93] and steroid-resistant sarcoidosis.[94]

DISCUSSION

The studies included in this review describe the wide range of off-label uses of baricitinib in dermatology. JAK inhibition is a therapeutic approach that has previously been used in treating dermatological conditions through blocking the downstream effects of the JAK-STAT signaling pathway. Through its targeting of JAK1 and JAK2, baricitinib, as described in this review, has been used in the treatment of connective tissue, eczematous, and vascular disorders, among other conditions that depend on JAK-STAT for pathogenesis.

Most off-label use has been described in the literature as case reports. However, clinical trials exist for the use of baricitinib in systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), AD, giant cell arteritis, and psoriasis. Further sufficiently powered and randomized studies investigating the safety, efficacy, and tolerance of baricitinib, including at different doses, are needed to better understand the potential role of baricitinib in treating off-label dermatological conditions.

DISCLOSURES

The authors have no conflicts of interest or financial disclosures, and all authors had access to the data and a role in writing the manuscript.

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Review of Superficial Cryotherapy for the Treatment of Alopecia Areata

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ABSTRACT

Cryotherapy has recently been examined as a potential treatment for alopecia areata (AA). AA is classically managed with intralesional or systemic steroids but relapse rates among those with longstanding disease are high. This narrative review serves to describe the existing studies evaluating cryotherapy for the treatment of AA and examine studies comparing cryotherapy with intralesional steroid injection for the treatment of AA. A review of the literature from 1990 to 2022 was conducted looking for keywords such as "alopecia areata" and "cryotherapy". A total of 8 studies were identified. Three studies assessed the efficacy of liquid nitrogen cryotherapy for the treatment of AA and found approximately 60% of patients responded to treatment and achieved hair regrowth. Three studies compared cryotherapy with intralesional corticosteroid injection, and 2 studies compared cryotherapy with topical corticosteroid therapy. There was no statistically significant difference in efficacy, but there is some evidence to suggest that relapse rates were lower in the cryotherapy group. Treatment protocols differed between studies regarding the number of cycles used for cryotherapy, dosage of intralesional steroids, and patient populations used. Some studies examined cases of recalcitrant AA while other studies examined all cases of AA. More research with larger sample sizes and with similar experimental procedures is necessary to assess the clinical efficacy of cryotherapy.

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INTRODUCTION

Alopecia areata (AA) is an autoimmune hair loss disorder arising due to loss of hair follicle immune privilege.[1] Increased antigen presentation at the bulb of the hair follicle leads to recruitment of various immune cells including $CD8^+$ cytotoxic T cells and natural killer (NK) cells. The subsequent release of numerous inflammatory mediators causes hair follicle destruction and further antigen presentation, thus feeding a perpetuating cycle resulting in clinical hair loss. Treatments for AA target the inflammatory aspect of the disease, such that prevention of further inflammatory destruction allows for the restoration of the hair follicle immune privilege and therefore cessation of the destructive autoimmune cycle. These treatments have traditionally included local and systemic corticosteroids, immunomodulatory agents (ie, janus kinase [JAK] inhibitors, calcineurin inhibitors, anthralin, etc.), and excimer laser.[2] However, no treatment modality is curative and relapse rates remain high. The purpose of this narrative review is to examine localized cryotherapy as a low-tech therapeutic option for patients with AA and compare its efficacy with that of other local treatments, including intralesional steroids as the current standard of care.[3]

Steroid and Other Therapeutics for Alopecia Areata

Traditional therapies for AA have been aimed at treating active disease and reducing relapse. Time of active disease correlates with probability of relapse with rates of ~13%, ~65%, and ~100% for patients with <6 months, 6 to 12 months, and >12 months active disease, respectively.[4]

First-line therapy for localized AA remains intralesional corticosteroid injection with triamcinolone acetonide.[5] A meta-analysis found 81% and 77% of subjects having hair regrowth following injections of 5 mg/mL and 10 mg/mL of triamcinolone acetonide, respectively.[6] Subjects were treated every 3 weeks or monthly intervals, for either 6 weeks (1 study), 12 weeks (4 studies), or 6 months (2 studies). The main adverse effect was skin atrophy, seen in 20% of patients treated with a higher concentration of 10 mg/mL.[6]

Topical steroids are also mainstay treatments for AA. Tosti et al found that treatment with topical clobetasol propionate 0.05% ointment under occlusion nightly for 6 days a week for 6 months yielded hair regrowth in 8 of 28 (30%) patients.[7] However, only 5 of 28 (17.8%) patients had long-term benefits without relapse.

Other studies have shown that topical desoximetasone 0.25% cream showed promising results with some cases of complete hair regrowth.[5] Relapse rates following cessation of topical treatment were found to vary between 37% and 63%.

Other agents have been investigated for the treatment of AA but remain uncommonly used for various reasons. Calcineurin inhibitors have been investigated for the treatment of AA. Both tacrolimus and pimecrolimus showed promising results as topical agents when used in animal models, but these results failed to translate in clinical trials involving patients with AA.[8]

Similar results were observed in trials investigating anthralin, a hydroxyanthrone anthracene derivative. Despite successful results in animal models, the drug failed to achieve acceptable results in patients with AA.[8] The JAK inhibitor baricitinib has only been recently approved for the treatment of AA by the US Food and Drug Administration. It has shown great efficacy, with 32.6% of patients with moderate to severe AA who were treated with 4 mg of Baricitinib once daily achieving at least 80% scalp hair coverage at week 36, as compared with 3% of patients in the placebo arm.[9] Nevertheless, safety and adverse effects remain a major concern with the use of baricitinib and the drug comes with a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.[10] Thus, there remains a great need for other effective treatment modalities for AA.

MATERIALS AND METHODS

Literature Search

A literature search in September 2022 was performed using the PubMed, EMBASE, and MEDLINE databases. Clinical studies that assess the use of liquid nitrogen cryotherapy with or without intralesional steroid for the treatment of alopecia areata were included. The databases were searched using different combinations of the following keywords: cryotherapy, alopecia areata, hair loss, intralesional steroid, and combined therapy. Roughly 1800 results were found and examined for relevance. Studies were chosen based on good clinical design and pertinence to the topic of interest. Of the 1800 published articles, 25 were selected for possible inclusion in this review. After reviewing the types of cryotherapy and the method of administration, the authors chose to omit 17 of the studies due to differences in type of cryotherapy administered. Eight studies were chosen to include in this review, some examined only cryotherapy for the treatment of AA, while others compared superficial cryotherapy with intralesional steroid, and some examined both superficial cryotherapy with intralesional steroid injection.

Cryotherapy for Alopecia Areata

Cryotherapy is an existing treatment used for a variety of dermatological conditions such as verruca vulgaris and basal cell carcinoma mainly due to its destructive property.[11] However, cryotherapy also exhibits immunomodulatory properties. In vivo studies revealed cryotherapy to reduce IL-17 release by T lymphocytes and to reduce T cell activation through reduced IL-1β/IL-23.[12,13] A hypothermic microenvironment also leads to decreased lymphocyte proliferation, cytotoxic CD8+ T cell function, and expression of interferon-gamma (IFN-γ) and IL-2.[14] Furthermore, Lei et al postulated that superficial cryotherapy could induce reactive vasodilation after the immediate initial vasoconstrictive response and improve microcirculation in hair follicles leading to increased hair growth.[15] The immunomodulatory and vascular effects of cryotherapy have made it an attractive low-cost and safe potential therapeutic modality for AA. Outcomes of clinical studies focused on cryotherapy for AA are reviewed next (Table 1).

Efficacy of Cryotherapy Monotherapy for Alopecia Areata

Jun et al performed a retrospective review of 353 subjects with AA treated with superficial cryotherapy consisting of liquid nitrogen sprayed on patches of AA 3 to 4 times each session every 2 weeks for 3 months.[16] Seventy-nine (~23%) subjects had >60% terminal hair regrowth and 136 subjects (~39%) had <60% of regrowth in alopecic lesions. When stratifying by affected scalp surface area, subjects with 25% to 50% scalp involvement demonstrated greater response (82.0%) compared with subjects with more severe disease involving ≥50% of the scalp with 17.0% being responders. With respect to adverse effects, only 18 (5.1%) of all treated subjects reported adverse effects consisting of mild pain, pruritis, or swelling. All symptoms resolved within 48 hours after treatment without intervention.

Zawar et al examined the efficacy of cryotherapy with liquid nitrogen in 11 subjects with recalcitrant AA.[17] Recalcitrant AA was defined as lack of therapeutic benefit with various treatment modalities over 6 months. Subjects were treated every 2 weeks for a maximum of 8 weeks and followed for 2 months after their last cryotherapy treatment. Each subject was treated with dual freeze and thaw cycles of 15s each. A total of 10 subjects completed the study and all exhibited some degree of regrowth. 50% demonstrated excellent response (defined as greater than 75% regrowth of terminal hairs) while 30% of patients reported a satisfactory response (defined as 51–75% regrowth of terminal hairs). Only 1 subject reported a poor response with less than 25% regrowth. Adverse effects, which included erythema and edema, were minimal and self-limited.

The efficacy of superficial cryotherapy with liquid nitrogen was also evaluated by Abdel-Majed et al in 17 participants with recalcitrant AA.[18] Participants underwent weekly cryotherapy once a week for 6 weeks. Each lesion was sprayed for 2 to 3 seconds and thawed for 3 to 5 seconds, followed by another cycle with the same parameters. Thirteen lesions (65.0% of lesions) responded to treatment with at least 25% of terminal

TABLE 1.

Summary of Studies Evaluating Superficial Cryotherapy for the Treatment of Alopecia Areata

Reference	Patient Population	Experimental Groups	Assessment	Results
Cryotherapy Monotherapy				
Jun et al	353 patients (all AA including totalis and universalis)	**Superficial cryotherapy** Liquid nitrogen (LN) spray (Cryopro) for 2-3 seconds for 3-4 rounds on all AA patches every 2 weeks. Primary endpoint was 3 months after the first treatment	**At month 3** **Marked recovery group** Regrowth of terminal hair in ≥60% of AA patches + recovery maintenance ≥1 month **Partial recovery group** Regrowth of terminal hair in <60% of AA patches **Poor recovery group** Limited to vellus hair regrowth	**Responders** Overall: 215 (60.9%) Marked recovery: 79 (22.4%) Partial recovery: 136 (38.5%) **Non-responders** Poor recovery: 85 (24.1%) No recovery: 53 (15.0%)
Zawar et al	11 patients with recalcitrant AA	**Superficial cryotherapy** LN for 15 seconds followed by 15 seconds of thawing for as many cycles until frost was observed. Patients treated every 2 weeks for a total of 5 sessions over 2 months (week 0, 2, 4, 6, and 8)	**At month 4** **Excellent response** Regrowth ≥ 75% **Satisfactory response** Regrowth 51–75% **Fair response regrowth** 26–50% **Poor response** Regrowth 11–25% **No response** Regrowth < 10%	**Drop out** 1 patient **Responders (10)** Excellent: 5 (50.0%) Satisfactory: 3 (30.0%) **Non-responders** Fair response: 1 (10.0%) No response: 1 (10.0%) **Notes** All responders showed sustained regrowth of hair at the end of 16 weeks except one patient who showed no response
Abdel-Majid et al	17 patients with 20 lesions of recalcitrant AA	**Superficial cryotherapy** LN once weekly for 6 weeks. Cryogun for 2–3 s until mild frost. Then thawed (~3–5 s), a second spray was done	**At week 6** **Excellent response** Regrowth ≥ 75% **Good response** Regrowth 50–75% **Moderate response regrowth** 25–50% **Poor response** Regrowth <25%	**Responders** Excellent response: 5 (25.0%) Good response: 6 (30.0%) Moderate response: 2 (10.0%) **Non-responders** Poor response: 4 **Notes** Superior clinical response observed (84.6%) with disease duration <6 months
Cryotherapy vs Intralesional Steroid Injections				
Sardana et al	100 patients with AA	**Arm I:** **Superficial cryotherapy** LN sprayed until frost was observed. Followed by one freeze–thaw cycle lasting 3–5 s. **Arm II:** **Intralesional steroid:** 10 mg/mL for a maximum of 3 mL (maximum volume of 3 mL per session) injected, every 4-6 weeks for 3 months	**At month 3** **No response** Regrowth 0–30% **Mild response** Regrowth 30–60% **Moderate response** Regrowth 60–90% **Complete response** Regrowth 90–100%	**Response rate** Arm I: 16.0% Arm II: 22.0 % *P*-value=0.002 **Notes** Superior increase in hair density increased with intralesional steroid as compared to superficial cryotherapy *P*-value=0.002 Higher rates of inflammation, mild itching, pain, pruritus, and swelling observed with superficial cryotherapy *P*-value=0.002

TABLE 1. (CONTINUED)

Summary of Studies Evaluating Superficial Cryotherapy for the Treatment of Alopecia Areata				
Reference	**Patient Population**	**Experimental Groups**	**Assessment**	**Results**
Cryotherapy vs Intralesional Steroid Injections				
Amirnia et al	240 patients with AA	**Arm I (N=120):** **Intralesional steroid:** 5 mg/ml triamcinolone acetonide per session. Patients treated for a total of 4 sessions over 12 weeks **Arm II (N=120):** Superficial cryotherapy: LN spray for 3-5s for a total of 2 cycles each one. Patients were treated for a total of 4 sessions over 12 weeks	**At weeks 3, 6, 9, and 12** **No response** Regrowth 0-30% **Mild response** Regrowth 30-60% **Moderate response** Regrowth 60-90% **Complete response** Regrowth 90-100%	**Arm I:** **Responders** Complete: 68 (56.7%) Moderate: 32 (26.7%) Non-responders No response: 20 (16.7%) **Arm II:** **Responders** Moderate: 40 (33.3%) Complete: 28 (23.3%) **Non-responders** No response: 52 (43.3%) **Notes** More patients treated with intralesional steroids achieved a complete response rate (P<0.05)
Hamdy El Sayed et al	21 patients with patchy AA	**Split-body design** **Lesion 1:** **Superficial cryotherapy** LN for 2-3 sec for 3-4 cycles, every 2 weeks over 3 months **Lesion 2:** **Intralesional steroids** 1mL of Triamcinolone acetonide (5 mg/ml) once every 1 month over 3 months	**At month 4** **Excellent response** Regrowth >75% **Moderate response** Regrowth 50%–75% **Mild response** Regrowth 20%–50% **Poor response** Regrowth 0%–20%	**Lesion 1:** **Responders** Excellent: 2 (10.0%) Moderate: 3 (15.0%) Mild: 11 (55.0%) **Non-responders** Poor: 4 (20.0%) **Lesion 2:** **Responders** Mild: 10 (50.0%) **Non-responders** Poor: 10 (50.0%) **Notes** Superior clinical improvement was observed with superficial cryotherapy as compared with intralesional steroids (P=0.002)
Cryotherapy vs Topical Steroids				
Faghihi et al	40 patients with AA	**Split-body design** **Lesion 1:** **Superficial cryotherapy** LN cryotherapy once weekly over 6 weeks **Lesion 2:** **Topical steroids** Topical betamethasone 0.1% lotion twice daily for 6 weeks	**At weeks 2 to 14, every 2 weeks** **Good response** Regrowth >75% **Moderate response** Regrowth 50-75% **Poor response** Regrowth 25-50% **No response** Regrowth < 25%	**Lesion 1:** **Responders** Good response 23.0% Moderate response 33.5% **Non-responders** Poor response: 31.5% No response: 12.0% **Lesion 2:** **Responders** Good response: 28.0% Moderate response: 34.5% **Non-responders** Poor response: 27.5% No response: 10.0% **Notes** Higher recurrence observed with topical betamethasone (68.0%) compared with superficial cryotherapy (41.0%)

TABLE 1. (CONTINUED)

Summary of Studies Evaluating Superficial Cryotherapy for the Treatment of Alopecia Areata				
Reference	**Patient Population**	**Experimental Groups**	**Assessment**	**Results**
Cryotherapy vs Topical Steroids				
Jun 2 et al	19 patients with AA with bilateral scalp patches	**Split-body design** **Lesion 1:** **Superficial cryotherapy + Topical steroids** LN for 2-3 seconds for 3-4 cycles. Patients treated twice a week for 4 months + Prednicarbate 0.25% twice a day for 4 months **Lesion 2:** **Topical steroids only** Prednicarbate 0.25% solution twice a day for 4 months	**4 months** Severity of Alopecia Tool (SALT) by 3 physicians **Phototrichoscopy:** changes in terminal and vellus hair and hair thickness **Responder:** hair regrowth was observed at or before (4 months after starting superficial cryotherapy) and maintained for ≥1 month	**4 patients dropped out** **11 Responders:** Terminal hair regrowth of terminal hair & maintained for ≥1 month: 11 (73.3%) (11 of 15), **4 non responders:** **Notes** No statistically significant difference in SALT scores between both treatment groups

hair regrowth. AA lesions smaller than 3 cm exhibited better response with 76.5% exhibiting improvement. Five lesions (25.0%) achieved greater than 75.0% regrowth, with 2 lesions achieving complete hair regrowth. Notably, participants with active disease of duration <6 months exhibited greater treatment response as compared with those with disease duration of >=6 months. The overall response rate observed by Abdel-Majed et al (65.0%) is similar to that observed by Jun et al (60.9%).

Superficial Cryotherapy Combined with Topical Steroid Treatment

Jun et al performed a split scalp study in 19 subjects with bilateral AA.[19] Subjects applied 0.25% prednicarbate solution to lesions on both sides of the scalp and underwent additional treatment with liquid nitrogen superficial cryotherapy on the right side of the scalp every 2 weeks for 4 months. Subjects were assessed using the Severity of Alopecia Tool (SALT) and phototrichoscopy. Eleven subjects (73.3%) demonstrated regrowth of terminal hairs on the side treated with combination therapy. A decrease in the SALT score was observed in both treatment groups (17.4% and 13.0% in the combination and monotherapy groups, respectively), but the difference was not statistically significant. Terminal hair count also increased 1.6-fold in the combination therapy group compared with the control (P=0.005). The study did not report any adverse effects in either treatment group.

Superficial Cryotherapy vs Intralesional or Topical Steroid

A prospective head-to-head study by Sardana et al compared the efficacy of intralesional triamcinolone acetonide 10 mg/mL injections (maximum volume of 3 mL per session) vs superficial cryotherapy in 100 subjects with patchy AA.[20] Subjects underwent treatment for 4 to 6 weeks and were followed-up for a total of 3 months after treatment completion. Overall response rates were 86% and 62% for the intralesional steroid and cryotherapy groups, respectively. Stratification by response type revealed higher rates of excellent response, defined as 90% to 100% hair regrowth, with the use of intralesional steroid (44%) as compared with cryotherapy (18%). Interestingly, disease relapse rate was greater in the group treated with intralesional steroids (22%) as compared with the one treated with cryotherapy (16%). In addition, higher rates of adverse effects including burning, pruritis, and pain were observed with intralesional steroids relative to superficial cryotherapy.

A larger retrospective analysis performed by Amirnia et al assessed 240 subjects with AA split into 2 treatment arms: intralesional triamcinolone acetonide 5 mg/mL and superficial cryotherapy with liquid nitrogen.[21] Subjects in both groups received the assigned intervention every 3 weeks for a total of 4 sessions over 12 weeks. Time-to-treatment-response was statistically significantly different between the intralesional steroid and superficial cryotherapy groups (4 weeks vs 6 weeks, respectively (P=0.001)). A complete response to treatment, defined as 90% to 100% scalp hair regrowth, was observed in 68 (56.7%) participants receiving intralesional steroid compared with 28 (23.3%) subjects receiving cryotherapy. While intralesional steroid therapy was more effective than cryotherapy in this study, complications were nearly twice as prevalent and consisted mainly of pain and localized skin atrophy.

Faghihi et al compared the efficacy of cryotherapy with liquid nitrogen to that of topical steroids in 40 subjects with patchy recalcitrant AA.[22] Each subject underwent cryotherapy once weekly for 6 weeks on one lesion and applied topical betamethasone 0.1% lotion daily for 6 weeks on another lesion. 23.0% of lesions receiving cryotherapy demonstrated >75% terminal hair regrowth compared with 28.0% of lesions receiving betamethasone, but no statistical significance was observed.

The recurrence rate however was significantly less in the cryotherapy group (41.0%) compared with the betamethasone group (68.0%).

An intra-patient comparative study by El Sayed et al assessed 21 subjects with patchy AA receiving either cryotherapy or intralesional steroid injection.[23] One AA patch underwent superficial liquid nitrogen cryotherapy every 2 weeks for 3 months (7 total sessions) while another patch received a single 1 mL injection of intralesional triamcinolone acetonide (5 mg/mL) once a month for 3 months. Response was assessed one month after the final treatment (week 16). Clinical improvement was statistically significantly higher in the cryotherapy group compared to the steroid group. 50.0% of lesions treated with steroid reported less than 20% regrowth (poor response), while only 20.0% of cryotherapy lesions showed poor response. On trichoscopic evaluation, there was no significant difference in terminal hair count but a trend toward higher counts was noted in the cryotherapy group. Lesions treated with cryotherapy however exhibited a significantly greater vellus hair count.

Other Studies Examining Cryotherapy for the Treatment of Alopecia Areata

Abdel Motaleb et al evaluated the clinical efficacy of various freezing times with cryotherapy with liquid nitrogen in 75 subjects with recalcitrant AA.[24] Subjects were divided into 3 groups based on freezing times: 3-5 seconds (Group A), 8-10 seconds (Group B), or 13-15 seconds (Group C). All subjects were treated with cryotherapy every 2 weeks for a maximum of 6 sessions and followed up at 4 months post treatment. Clinical response was evaluated using serial photographs and trichoscopy. All treatment groups resulted in hair regrowth but were not significantly different between groups. Mean percentage of improvement was noted to be highest in Groups B (72.4%) and C (71.7%) compared with Group A (55.9%). Relapse rates were 22.0%, 12.0%, and 9.5% in Group A, B, and C, respectively. Group C did report the highest number of adverse effects, as expected given the long duration of freezing time, with 52.0% of patients experiencing vesiculations and erosion in the treatment area.

Sayed et al compared superficial liquid nitrogen cryotherapy to topical psoralen and ultraviolet A (PUVA) in 52 subjects.[25] Subjects undergoing cryotherapy received treatment every 2 weeks for a maximum of 6 sessions. Subjects who underwent treatment with PUVA received treatment twice weekly for 6 weeks. The UVA starting dose began at 0.25-0.5 J/cm^2 and increased incrementally until a max dose of 8 J/cm^2 was reached. Patients were evaluated before each treatment and 12 weeks after the last treatment. 80% of subjects achieved 50% to 100% hair regrowth in the PUVA group whereas 63% of cryotherapy patients demonstrated the same improvement. The cryotherapy group showed a slightly higher recurrence rate (15%) compared with the PUVA group (8.7%). No adverse effects were reported.

Nouh et al examined fractional carbon dioxide (CO_2) laser vs liquid nitrogen cryotherapy in 80 participants with AA.[26] Forty participants were treated with fractional CO_2 laser every 2 weeks for 4 sessions, and 40 participants were treated with liquid nitrogen spray every 2 weeks for 4 sessions. All participants demonstrated improvement. Twenty-six (65.0%) participants in the cryotherapy group demonstrated >= 25% regrowth at 3 months after administration of the final treatment while 33 (82.5%) participants in the CO2 laser group demonstrated >= 25% regrowth. However, this difference was not statistically significant (P=0.095). There was no statistically significant difference between the 2 groups on trichoscopy evaluating changes in number of yellow dots, vellus hair, broken hairs, or circle hairs. No serious adverse effects were reported in either group.

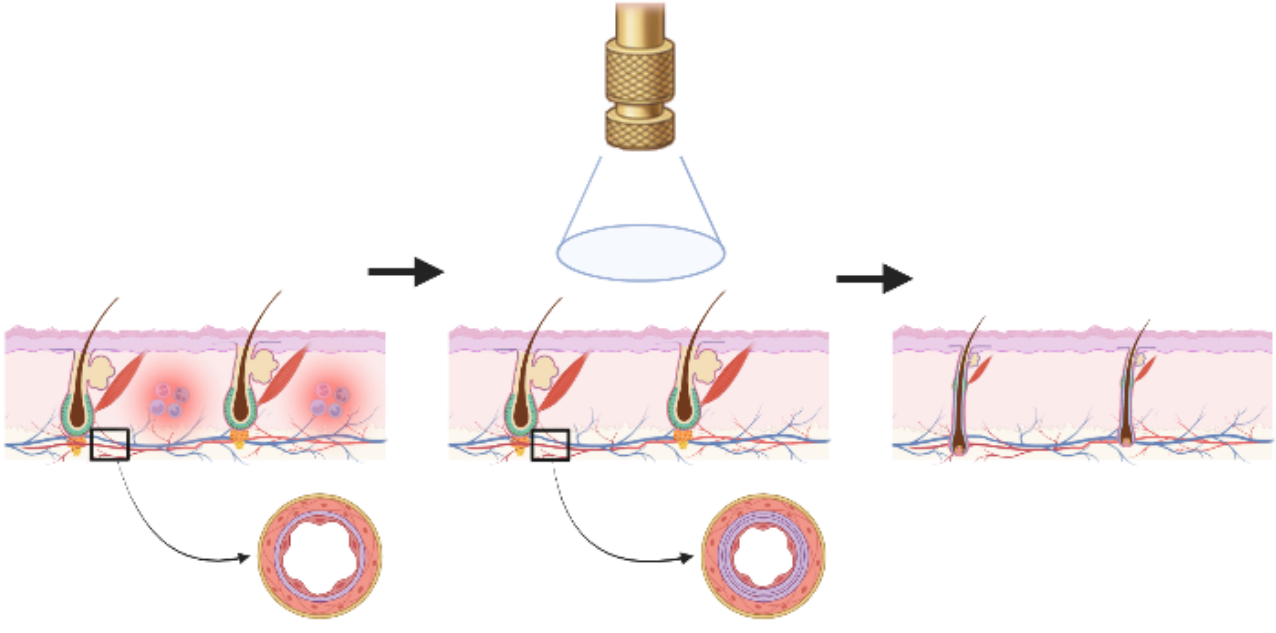
DISCUSSION

Alopecia areata affects 2% of the general population and accounts for nearly 25% of all cases of hair loss disorders.[27] The complex pathophysiology of AA has not been elucidated so far but mounting evidence has confirmed immune cell dysfunction and loss of hair follicle immune privilege to be major contributors to its development. As such, in the absence of curative treatment for this disorder, management revolves around local and systemic immunomodulatory therapy. Aberrant $CD4^+$ and $CD8^+$ T cell and NK cell activation with subsequent destruction of the hair follicle are likely mediators of AA, and the efficacy of systemic immunomodulatory treatments such as methotrexate, cyclosporine, and oral prednisolone strongly supports this proposed etiology.[5,28] Unfortunately, systemic immunosuppression is associated with sometimes severe adverse effects such as opportunistic infection, leukopenia, and gastrointestinal dysfunctuion, as well as high rates of relapse.[5,29] Local control of inflammation thus remains the mainstay of treatment.

Cryotherapy with liquid nitrogen is one such therapeutic modality that has shown efficacy in the treatment of AA. This safe, inexpensive, and very accessible therapy remains less widely utilized than steroidal agents in current practice. In this review, we sought to examine the literature reporting on the efficacy as well as influence on disease relapse of cryotherapy alone or in combination with intralesional or systemic corticosteroids.

The effect of cryotherapy for the treatment of AA was first examined in 1991, revealing that 97% of patients with mild AA treated with superficial liquid nitrogen cryotherapy demonstrated a therapeutic response.[15] Subsequent studies, outlined in Table 1, revealed response rates with 50% or more hair regrowth ranging between 55.0% and 80.0%, including in patients with recalcitrant AA. Patients were treated 4 to 6 times

FIGURE 1. Suggested mechanism of action of cryotherapy leading to conversion of hair follicle from the telogen phase to the anagen phase through blood vessel smooth muscle constriction and subsequent reduced blood flow to the hair bulb.



but received various doses at different frequencies. Additionally, relapse upon treatment cessation was not examined despite it being a common challenge in the therapeutic process.[30] In the studies directly comparing superficial cryotherapy with liquid nitrogen to intralesional steroid injection, regrowth rates were found to be similar amongst the 2 groups. Treatment with cryotherapy was reported to have a more favorable side effect profile. While the main adverse effect observed with intralesional steroid is dermal atrophy, this was not observed with the use of cryotherapy. In addition, relapse rates were found to be higher in patients treated with intralesional steroids. Therefore, cryotherapy appears as a good alternative to intralesional steroids, given the similar rates of efficacy, improved side effect profile, and longer lasting results. It also appears to be a superior alternative to topical steroids, given its enhanced clinical efficacy and lower rates of relapse (Table 1).

These findings pertaining to the observed clinical response might be explained by the hypothesized mechanism of action of cryotherapy in AA. Vasoconstriction secondary to tissue freezing and immunomodulation, through subsequent increased permeability of endothelial cells in microcirculatory vessels promoting reduced local inflammation and subsequent restoration of hair follicle immune privilege, a key factor in AA pathogenesis, may together promote hair follicle regrowth (Figure 1). However, this remains to be investigated further. Future studies with longer follow-up duration are also needed to better understand the clinical picture and also help quantify relapse rates and durations of sustained hair regrowth. An additional limitation to the current literature found in many of the reported studies is lack of statistical significance, which is likely due to limited patient sample size, calling for future studies to include a larger number of patients.

The low cost and ease of availability of cryotherapy makes a strong case for further investigations for its use as part of the routine therapeutic armamentarium for AA, in both treatment-naïve patients and those who have failed or experience side effects with the gold-standard use of steroids. Indeed, most studies looking at its efficacy included patients with recalcitrant AA and showed promising results. Building on the latter, studies investigating combination treatment including cryotherapy as one of the modalities should be conducted to assess for synergistic effects in patients with unresponsive AA. This could perhaps lead to a treatment paradigm with reduced treatment failures or relapse rates that could help overcome recalcitrance. Additionally, cryotherapy appeared equivalent in efficacy to both PUVA and CO2 laser, 2 modalities with a much higher out-of-pocket cost to patients, an important consideration given the high financial burden from covering medical costs that patients with AA face.[31,32]

Given the lack of consistency across the regimens investigated, it is hard to recommend a certain therapeutic protocol to follow for the use of cryotherapy for AA. It remains important to note that the literature showed efficacy with a minimum of 4 treatments involving at least 1 freeze-thaw cycle. In addition, increased hair regrowth and lower relapse rates were observed

with freezing times lasting at least 8 seconds. Further trials investigating various regimens involving cryotherapy for AA, either as monotherapy or part of a multimodal approach, are needed. Additionally, cryotherapy could be investigated in the pediatric population as a less painful alternative to intralesional steroid injection. Given the long interval between treatments and more tolerable side effect profile, examining superficial cryotherapy in pediatric patients could provide a valuable alternative treatment.

DISCLOSURES

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

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ORIGINAL ARTICLE

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Long-Term Safety and Efficacy of Twice-Daily Topical Clascoterone Cream 1% in Patients ≥ 12 Years of Age With Acne Vulgaris

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ABSTRACT

Background: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged ≥ 12 years based on results from two 12-week Phase 3 studies in patients with moderate-to-severe acne. Safety and efficacy of clascoterone in patients aged ≥ 12 years from an open-label, long-term extension study are presented.

Methods: Enrolled patients applied clascoterone cream 1% twice daily to the entire face and, if desired by the patient and/or investigator, truncal acne, for up to 9 months. Patients achieving Investigator's Global Assessment score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened. Safety was assessed from treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs [telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus]) in all treated patients. Efficacy was assessed from IGA at each visit among those completing the study per-protocol (PP); face and trunk were evaluated individually.

Results: Of 600 patients aged ≥ 12 years (original randomization: 311 clascoterone, 289 vehicle), 343 completed the extension study (177 clascoterone, 166 vehicle). There were 187 TEAEs in 108/598 clascoterone-treated patients (18.1%), including 56/311 (18.0%) and 52/287 (18.1%) patients originally randomized to clascoterone and vehicle, respectively; the most common LSRs (previous clascoterone/vehicle) were erythema (face, 8.0%/7.7%) and scaling/dryness (face, 10.0%/7.3%). The percentage of PP patients with facial and truncal IGA 0/1 increased to 48.9% (156/319) and 52.4% (65/124), respectively, at study end.

Conclusions: Clascoterone cream 1% maintained a favorable safety and efficacy profile for up to 12 months in patients aged ≥ 12 years.

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INTRODUCTION

Acne vulgaris is a chronic skin condition characterized by excess sebum production, hyperkeratinization, *Cutibacterium acnes* colonization, and inflammation.[1] Acne vulgaris affects approximately 85% of adolescents and young adults between 12 and 25 years of age, attributable in part to the influence of pubertal hormonal changes, but can also persist into adulthood.[2] Androgens such as dihydrotestosterone (DHT) play a key role in driving acne pathogenesis via expression of genes that mediate sebum production and inflammation.[2-4] Antiandrogen medications for acne vulgaris include off-label use of spironolactone and combined oral contraceptives,[3,5] although these medications are not suitable for use in males.[3] Long-term spironolactone treatment is also associated with a potential risk of hyperkalemia, and laboratory monitoring is recommended, particularly for patients with impaired renal function or concomitant use of drugs that elevate potassium levels.[6]

Clascoterone cream 1%, a novel topical androgen receptor inhibitor,[7] was approved in the US in 2020 for the treatment of acne vulgaris in males and females ≥ 12 years of age.[8] Clascoterone has a steroidal structure similar to DHT and inhibits the binding of DHT to androgen receptors in vitro.[9,10] Clascoterone is rapidly hydrolyzed to cortexolone, a primary inactive metabolite, resulting in low quantifiable plasma levels of clascoterone after topical application, and therefore, low systemic exposure.[11,12] The efficacy and safety of clascoterone were assessed in 2 identical Phase 3 clinical trials and a long-term extension study in patients ≥ 9 years of age with moderate-to-severe acne vulgaris.[1,7] In the Phase 3 pivotal studies, treatment with clascoterone cream 1% resulted in significant clinical improvement compared with vehicle cream after 12 weeks of twice-daily application, with a favorable safety profile.[1] Clascoterone safety was well maintained for up to an additional 9 months of treatment in patients ≥ 9 years old with moderate-to-severe acne vulgaris.[7] Here, we present long-term

safety and efficacy data in the subgroup of clinical trial patients ≥ 12 years old who entered the long-term extension study.

MATERIALS AND METHODS

Study Design and Patients

The multicenter, open-label, long-term safety study of clascoterone cream 1% in patients with moderate-to-severe acne vulgaris ≥ 9 years of age (www.clinicaltrials.gov NCT 02682264) was previously described in detail.[7] The original study was conducted in accordance with principles of the Declaration of Helsinki, the current Good Clinical Practice guidelines, and all country-specific regulatory requirements. Institutional Review Board approval was obtained for the protocol and informed consent forms. Voluntary informed consent was given by every patient, and patients under the age of 18 years provided written informed consent and were accompanied by a parent or legal guardian; the parent or legal guardian also provided informed consent for the patient.

Patients completed one of the Phase 3 pivotal studies and enrolled within 3 days of the final pivotal study visit to be eligible for the extension study.[7] This analysis only included patients ≥ 12 years of age.

Treatments Administered

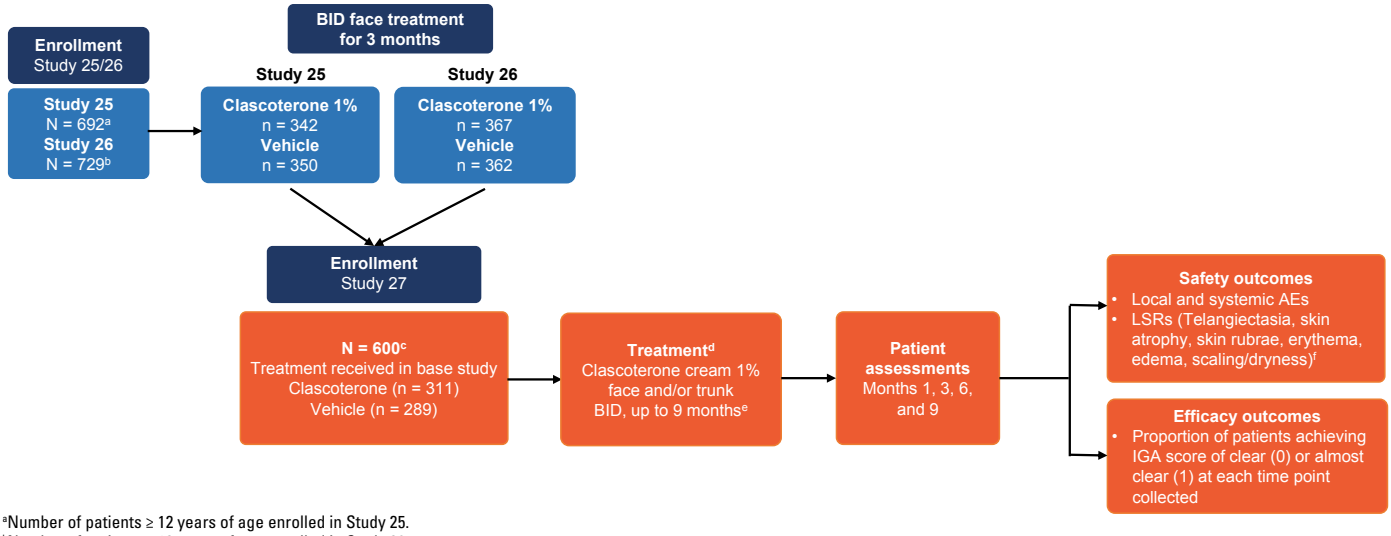
All patients applied clascoterone cream 1% twice daily to the entire face and, if desired by both patient and investigator, truncal acne for up to 9 additional months of treatment. Patients randomized to vehicle cream in the pivotal studies applied clascoterone cream in the long-term extension; patients originally randomized to clascoterone cream continued treatment. The maximum clascoterone treatment time in the pivotal and extension studies was 12 months for the face (3 months in the pivotal studies and 9 months in the extension study) and 9 months for the trunk. Patients who achieved Investigator's Global Assessment (IGA) score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened (Figure 1).

Assessments and Outcomes

Safety and efficacy were assessed at scheduled patient visits at months 1, 3, 6, and 9 (Figure 1).[7] As previously described,[7] primary safety endpoints included frequencies of local and systemic treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), and frequency and severity of local skin reactions (LSRs). The investigator evaluated the severity of telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness using a 5-point scale from 0 (none) to 4 (severe); patients were asked to rate the severity of stinging/burning and pruritus using a 4-point scale from 0 (none) to 3 (severe).

Efficacy was determined based on measurement of the overall severity of acne using the 5-point IGA, ranging from 0 (clear) to 4 (severe), which was assessed separately for the face and trunk at each study visit. The efficacy endpoint was the number of patients with each IGA severity score for each treatment area, as applicable, at each time point collected (baseline and long-term follow-up at months 1, 3, 6, and 9); the proportion of patients achieving IGA 0/1 for each treatment area is reported. The facial IGA score at the end-of-study visit of the Phase 3 study and the truncal IGA score during the first extension study visit were used as baseline data.

FIGURE 1. Study design.



[a]Number of patients ≥ 12 years of age enrolled in Study 25.
[b]Number of patients ≥ 12 years of age enrolled in Study 26.
[c]Number of patients ≥ 12 years of age enrolled in the long-term extension study (Study 27).
[d]Patients who achieved IGA score of ≤ 1 could stop treatment and resume if/when acne worsened.
[e]Total clascoterone treatment duration was up to 12 months for patients treated with clascoterone for 3 months in the pivotal studies.
[f]The severity of LSRs was assessed using a five-point scale from 0 (none) to 4 (severe).
AE, adverse event; BID, twice daily; IGA, Investigator's Global Assessment; LSR, local skin reaction.

Statistical Analysis

All statistical analyses were performed using SAS® for Windows version 9.3. For demographic, efficacy, and safety data, continuous variables were described by descriptive statistics and categorical data by frequency counts and percentages of patients within each category. Sample size calculations were previously described.[7] No interim analyses were performed. Missing data were not imputed.

Patient demographics are reported for the intention-to-treat (ITT) population, which included all enrolled individuals. Safety was assessed in all enrolled patients who received at least 1 application of clascoterone during the extension study (safety population). Efficacy was assessed in the per-protocol (PP) population, which included all patients who completed the extension study without significant protocol deviations; criteria for PP exclusion included failure to satisfy inclusion/exclusion criteria, use of prohibited medications, noncompletion of study, lack of compliance, or failure to treat individual with clascoterone.

As previously described,[7] all TEAEs were coded using the Medical Dictionary for Regulatory Activities version 18.1 and were listed by preferred term and system organ class.

RESULTS

Patients and Demographics

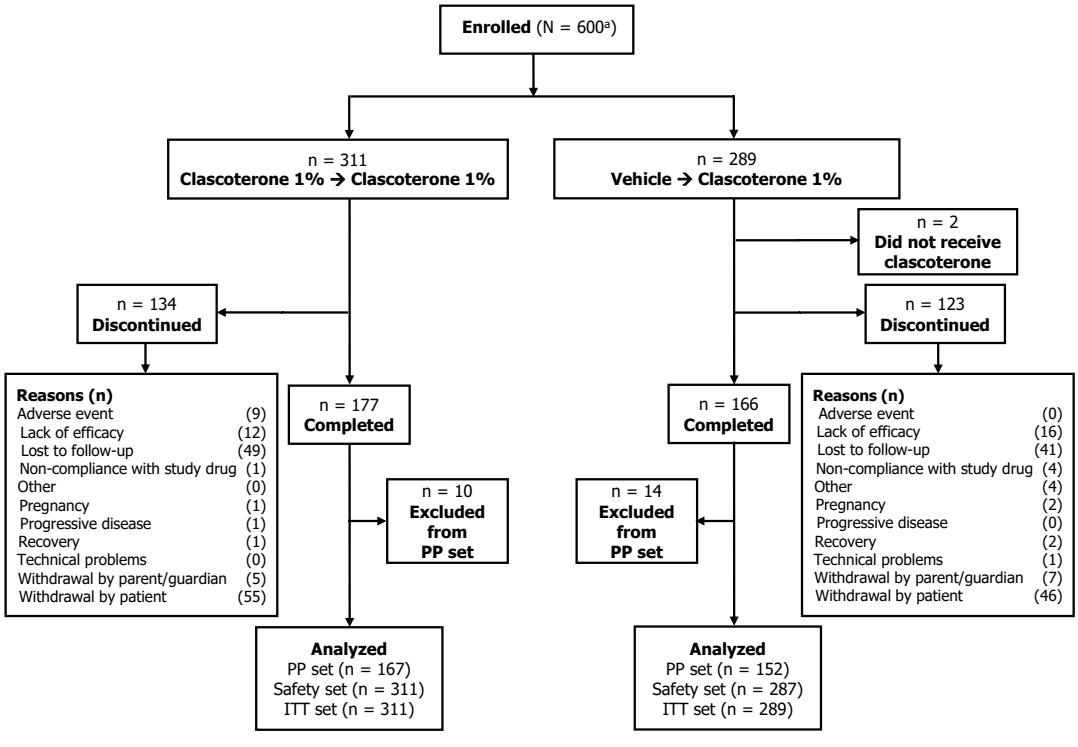
Of 609 patients who entered the extension study,[7] 600 were ≥ 12 years of age; of these, 311 were originally randomized to treatment with clascoterone and 289 to vehicle in the pivotal studies (Figure 2). The mean ± standard deviation age was 19.3 ± 6.2 in the ITT population (n = 600) and 19.8 ± 6.6 in the PP population (n = 319). The majority of patients were female (ITT, 62.2%; PP, 60.8%), and the population was predominantly White (Table 1). The safety population included 598 patients treated with clascoterone.

Patient disposition is shown in Figure 2. A total of 134 and 123 patients originally treated with clascoterone and vehicle, respectively, discontinued the study, most frequently because of patient withdrawal (55 [17.7%] and 46 [15.9%]) and loss to follow-up (49 [15.8%] and 41 [14.2%]). Overall, 245 patients in the safety population (126 originally randomized to clascoterone and 119 to vehicle) and 124 patients in the PP population (67 originally randomized to clascoterone and 57 to vehicle) treated truncal acne.

Treatment Exposure

During the extension study period, 184/598 (30.8%) patients in

FIGURE 2. Patient disposition.



[a]Number of patients ≥ 12 years of age enrolled in the long-term extension study.
Patients are summarized according to the original treatment they received in the Phase 3 pivotal studies. All patients in the long-term extension study applied clascoterone cream 1%.
ITT, intention-to-treat; PP, per-protocol.

TABLE 1.

Patient Demographics						
Characteristic	Clascoterone		Vehicle		Overall	
	ITT n = 311	PP n = 167	ITT n = 289	PP n = 152	ITT N = 600	PP N = 319
Sex						
Male	118 (37.9)	70 (41.9)	109 (37.7)	55 (36.2)	227 (37.8)	125 (39.2)
Female	193 (62.1)	97 (58.1)	180 (62.3)	97 (63.8)	373 (62.2)	194 (60.8)
Race						
Caucasian	279 (89.7)	157 (94.0)	257 (88.9)	134 (88.2)	536 (89.3)	291 (91.2)
Asian	5 (1.6)	2 (1.2)	8 (2.8)	5 (3.3)	13 (2.2)	7 (2.2)
Black or African American	16 (5.1)	5 (3.0)	16 (5.5)	9 (5.9)	32 (5.3)	14 (4.4)
Other	11 (3.5)	3 (1.8)	8 (2.8)	4 (2.6)	19 (3.2)	7 (2.2)
Ethnicity						
Hispanic or Latino	26 (8.4)	9 (5.4)	15 (5.2)	7 (4.6)	41 (6.8)	16 (5.0)
Not Hispanic or Latino	285 (91.6)	158 (94.6)	274 (94.8)	145 (95.4)	559 (93.2)	303 (95.0)
Age, years						
Mean	19.3	19.7	19.3	19.9	19.3	19.8
Median	17.0	18.0	17.0	18.0	17.0	18.0
Standard deviation	5.77	6.13	6.68	7.04	6.22	6.57
Range	12–50	12–50	12–50	12–50	12–50	12–50

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Data shown as n (%) unless otherwise specified.
ITT, intention-to-treat; PP, per-protocol.

the safety population were treated with clascoterone for facial acne for up to 3 months, 85/598 (14.2%) for 3 to 6 months, 176/598 (29.4%) for 6 to 9 months, and 153/598 (25.6%) for ≥ 9 months. Among patients treated with clascoterone for truncal acne, 70/245 (28.6%) were treated for up to 3 months, 31/245 (12.7%) for 3 to 6 months, 74/245 (30.2%) for 6 to 9 months, and 70/245 (28.6%) for ≥ 9 months. The amount of cream applied daily and total duration of exposure to clascoterone in the extension study were similar among patients previously treated with clascoterone vs vehicle in the pivotal studies. Patients originally randomized to clascoterone in the pivotal studies had 3 months of treatment with clascoterone for facial acne prior to entering the extension study.

Safety

Overall, 108/598 (18.1%) patients in the safety population experienced a total of 187 TEAEs, with similar frequency between patients previously treated with clascoterone (56/311 [18.0%]) vs vehicle (52/287 [18.1%]; Table 2). The majority of reported TEAEs were mild or moderate in severity, and most were not considered related to clascoterone treatment. A total of 6/598 (1.0%) patients reported SAEs, none of which was considered related to clascoterone treatment, and 9/598 (1.5%) patients had TEAEs leading to study discontinuation. The most frequent TEAEs by percentage of patients affected included nasopharyngitis (17 [2.8%]), upper respiratory tract infection (11 [1.8%]), sinusitis (5 [0.8%]), viral respiratory tract infection (5 [0.8%]), and application site acne (4 [0.7%]) among all patients; TEAE frequencies were similar among patients originally randomized to clascoterone compared with vehicle in the pivotal Phase 3 studies (Table 3). No deaths were reported during the study.

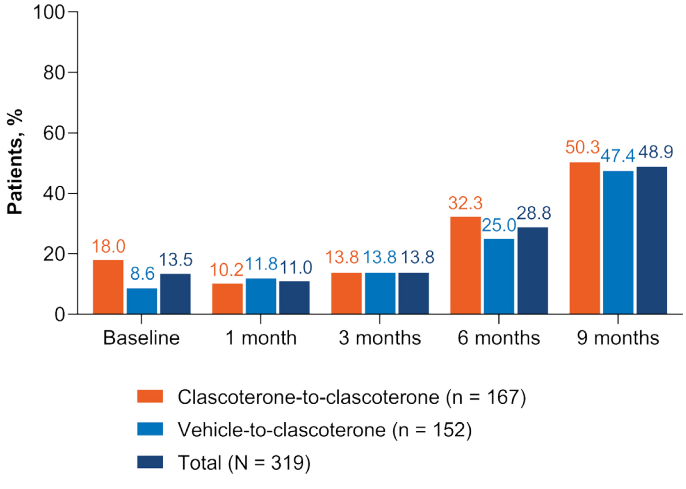
The frequency of LSRs was low throughout the study in patients previously treated with either clascoterone or vehicle. The most common new or worsening LSRs in patients previously treated with clascoterone/vehicle were scaling/dryness (face, 10.0%/7.3%; trunk, 3.5%/4.5%) and erythema (face, 8.0%/7.7%; trunk, 6.1%/7.3%; Table 4).

Efficacy

The percentage of PP patients who achieved facial IGA 0/1 (clear or almost clear) increased over time from 43/319 (13.5%) at baseline to 156/319 (48.9%) at the end of the study (9 months of treatment), with improvement observed at most visits (Figure 3). The percentage of patients with facial IGA 0/1 was higher at baseline in patients previously treated with clascoterone (30/167 [18.0%]) vs vehicle (13/152 [8.6%]) and increased over time in both cohorts to 84/167 (50.3%) and 72/152 (47.4%), respectively, at the end of the study.

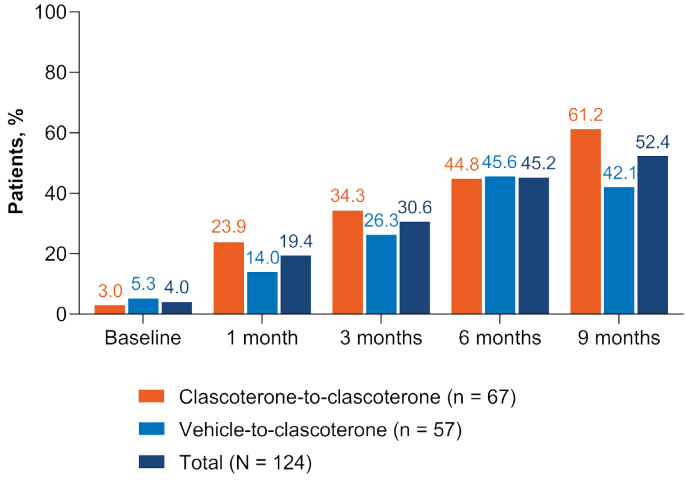
For truncal acne, the percentage of PP patients with truncal IGA 0/1 at baseline was low overall (5/124 [4.0%]) and increased to 65/124 [52.4%]) at the end of the study, with improvement

FIGURE 3. Percentage of patients ≥ 12 years of age with facial IGA 0/1 by visit.



Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Per-protocol population. Data shown as % unless otherwise specified.
All patients in the per-protocol population were assessed at all visits.
IGA 0/1, Investigator's Global Assessment score of 0 or 1.

FIGURE 4. Percentage of patients ≥ 12 years of age with truncal IGA 0/1 by visit.



Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Per-protocol population. Data shown as % unless otherwise specified.
All patients in the per-protocol population were assessed at all visits.
IGA 0/1, Investigator's Global Assessment score of 0 or 1.

TABLE 2.

Summary of TEAEs in Patients ≥ 12 Years of Age

Category	Clascoterone n = 311	Vehicle n = 287	Overall N = 598
Subjects with any TEAE	56 (18.0)	52 (18.1)	108 (18.1)
Mild	35 (11.3)	36 (12.5)	71 (11.9)
Moderate	27 (8.7)	23 (8.0)	50 (8.4)
Severe	4 (1.3)	3 (1.0)	7 (1.2)
Any test article–related TEAE	11 (3.5)	2 (0.7)	13 (2.2)
Any TEAE leading to discontinuation	9 (2.9)	0	9 (1.5)
Any serious TEAE	3 (1.0)	3 (1.0)	6 (1.0)
Any test article–related serious TEAE	0	0	0
Any serious TEAE leading to discontinuation	1 (0.3)	0	1 (0.2)
Any TEAE leading to death	0	0	0
Number of TEAEs, N	102	85	187
Related to test article	16	2	18
Not related to test article	86	83	169
Mild	55	53	108
Moderate	40	29	69
Severe	7	3	10

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
TEAE, treatment-emergent adverse event.

TABLE 3.

Most Frequent TEAEs in Patients ≥ 12 Years of Age

Most Frequent TEAEs	Clascoterone n = 311		Vehicle n = 287		Overall N = 598	
	Events, n	Patients	Events, n	Patients	Events, n	Patients
Application site acne	4	4 (1.3)	0	0	4	4 (0.7)
Nasopharyngitis	7	6 (1.9)	14	11 (3.8)	21	17 (2.8)
Respiratory tract infection viral	1	1 (0.3)	4	4 (1.4)	5	5 (0.8)
Sinusitis	3	3 (1.0)	2	2 (0.7)	5	5 (0.8)
Upper respiratory tract infection	9	8 (2.6)	3	3 (1.0)	12	11 (1.8)

Patients are summarized overall and according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
TEAE, treatment-emergent adverse event.

TABLE 4.

New or Worsening LSRs on the Face and Trunk in Patients ≥ 12 Years of Age

Symptom	Clascoterone n = 311		Vehicle n = 287	
	Face	Trunk	Face	Trunk
Edema	5 (1.6)	1 (0.3)	5 (1.7)	5 (1.7)
Erythema	25 (8.0)	19 (6.1)	22 (7.7)	21 (7.3)
Pruritus	13 (4.2)	5 (1.6)	16 (5.6)	4 (1.4)
Scaling/Dryness	31 (10.0)	11 (3.5)	21 (7.3)	13 (4.5)
Skin atrophy	3 (1.0)	1 (0.3)	4 (1.4)	4 (1.4)
Stinging/Burning	11 (3.5)	1 (0.3)	8 (2.8)	2 (0.7)
Striae rubrae	1 (0.3)	2 (0.6)	2 (0.7)	1 (0.3)
Telangiectasia	3 (1.0)	1 (0.3)	4 (1.4)	1 (0.3)

Patients are summarized according to the original treatment they received in the Phase 3 pivotal studies.
Safety population. Data shown as n (%) unless otherwise specified.
LSR, local skin reaction.

observed at each visit (Figure 4). The percentage of patients with truncal IGA 0/1 generally increased over time regardless of prior exposure to facial clascoterone treatment, although the greatest percentage was observed at the end of the study in patients originally randomized to clascoterone (41/67 [61.2%]).

Among the original study population of patients ≥ 9 years of age, the proportion of PP patients with clear or almost clear skin on the face and trunk at the end of the study was comparable to that observed in the subgroup of patients ≥ 12 years old (facial IGA 0/1, 156/324 [48.1%]; truncal IGA 0/1, 66/126 [52.3%] for patients ≥ 9 years old).

DISCUSSION

This 9-month extension study confirmed the favorable safety profile of clascoterone cream 1% in the long-term treatment of patients ≥ 12 years of age with moderate-to-severe facial and/or truncal acne vulgaris. The frequencies of TEAEs and LSRs were low throughout the study; most reported TEAEs were mild in severity, and there was no accumulation of AEs observed over time. The proportions of patients with facial and truncal IGA 0/1 increased over time and were highest at the end of the study, indicating that clascoterone efficacy continued to increase with long-term treatment. These results suggest that clascoterone may be a suitable option for long-term topical treatment of both facial and truncal acne vulgaris in patients ≥ 12 years of age.

The findings from this and previous studies support clascoterone as an option for long-term treatment of acne vulgaris. Systemic exposure is low following topical clascoterone treatment[12]; and systemic antiandrogen effects associated with oral androgen receptor blockers and other hormonal treatments[3] were not observed in patients treated with clascoterone cream 1% in this long-term study or previous studies.[1,12,13] Laboratory abnormalities were not evaluated in this study or the Phase 3 pivotal studies; shifts from normal to elevated potassium levels were observed in some patients treated with clascoterone in the Phase 1 and Phase 2 studies, although none were reported as AEs. Hypothalamic-pituitary-adrenal (HPA) axis suppression was observed in 3/42 (7%) patients treated with clascoterone in a Phase 2 safety study in patients ≥ 12 years of age with moderate-to-severe acne vulgaris; HPA axis function returned to normal in all patients at follow-up 4 weeks after stopping treatment.[12] During 9 additional months of clascoterone treatment, the most common new or worsening LSRs on both the face and trunk in

patients ≥ 12 years of age were erythema and scaling/dryness, consistent with previously published long-term findings in patients ≥ 9 years of age[7] and short-term studies.[1,13]

These findings expand upon results from the Phase 3 pivotal studies, in which clascoterone cream 1% was significantly more efficacious vs vehicle cream after 12 weeks of treatment.[1,14] In this long-term extension study, approximately half of PP patients ≥ 12 years of age achieved IGA 0/1 for both the face and trunk. The proportion of patients who were clear or almost clear increased at each visit and was highest at the end of the study, indicating that clascoterone efficacy improved over time for up to 12 months in patients with moderate-to-severe acne vulgaris.

The study was designed primarily to evaluate long-term safety, and therefore, there was no ongoing comparator planned for efficacy evaluation. Additionally, concomitant acne medications were not evaluated in this study; therefore, the safety and efficacy of combined treatment with clascoterone and other topical medications should be evaluated in future clinical studies.

CONCLUSION

Clascoterone cream 1% exhibited favorable long-term safety and efficacy during treatment up to 12 months in patients ≥ 12 years of age with moderate-to-severe acne vulgaris and may be a safe and effective alternative to traditional acne medications for long-term treatment.

DISCLOSURES

LFE, AAH, and LSG were study investigators. LFE, AAH, and LSG were also compensated advisors to Cassiopea. AAH is an employee of the McGovern Medical School of The University of Texas Health Science Center in Houston, which received compensation from Cassiopea S.p.A., for study participation; she also received an honorarium for serving on the Cassiopea advisory board; all research grant funds were paid to her institution. She has also received personal fees for advisory, speaking, consulting, and/or other services with Almirall, Incyte, Pfizer, Aslan, Galderma Laboratories, Novartis, and Sun Pharma. LFE is an employee of the University of California San Diego, which received compensation from Cassiopea S.p.A., for study participation; he has also served as an investigator, advisor, or consultant for Almirall, Dermata, Galderma Laboratories, and Ortho Dermatologics. LSG is an employee of the Henry Ford Health System in Detroit, Michigan, which received compensation from Cassiopea S.p.A., for study participation; she has also received personal fees for advisory, speaking, consulting, research, and/or other services with Almirall, Foamix, Galderma Laboratories, Novartis, Sol-Gel, and Sun Pharma. MC is employed as the Vice President of Medical Affairs at Novan Inc.; was employed as the senior director of medical affairs at Cassiopea, Inc. at the time of the study; received personal fees as a consultant from Cassiopea S.p.A.; and receives personal fees as an adjunct faculty member from the University of Arizona. LM is an employee of Cassiopea S.p.A., and holds stock options in the company. JH is an employee of Pharmapace Inc. NS is an employee of Sun Pharmaceutical Industries, Inc. AM is employed as the chief medical officer for Cassiopea S.p.A., and holds stock options in the company; and has served as the chief medical officer of Cosmo Pharmaceuticals.

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ORIGINAL ARTICLE

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Dermatology in Contemporary Times: Building Awareness of Social Media's Association With Adolescent Skin Disease and Mental Health

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ABSTRACT

Background: The contribution of psychological disorders to the burden of skin disease has been poorly explored in adolescent patients. The review aims to provide insights into the psychological, social, occupational, and social medias' association with acne, atopic dermatitis (AD), and aesthetics in adolescent patients.

Methods: The project used a modified Delphi process comprising face-to-face discussions followed up online. The systematic literature search results informed the 14 draft statements. During an expert panel meeting, the draft statements underwent the panel's evaluation at a workshop, followed by a plenary discussion adopting five statements using evidence from the literature coupled with the panel's opinions and experiences.

Results: Studies reported an association between poor sleep, social impairment, and mental health disorders, including body dysmorphic disorder (BDD) with acne or AD in adolescents with acne or AD. Education for patients and parents may improve self-management skills and self-responsibility, promoting better outcomes for acne and AD. The use of certain types of social media can contribute to unrealistic expectations regarding the outcomes of cosmetic procedures. Social media use may also be associated with, and potentially contribute to unrealistic appearance expectations and certain mental health conditions. However, social media use may have benefits, such as connection, diversity, social support, increased self-esteem, safe identity experimentation, and an increased opportunity for self-disclosure.

Conclusions: The association with negative life events, BDD, suicidal ideation, depression, and anxiety are thought to be high for adolescent patients with acne or AD. Using social media for information has both positive and negative aspects. Awareness of the risks and benefits of receiving health information about dermatological disease among adolescents needs to be improved through the education of patients and clinicians. Action-oriented items need to be developed to help dermatologists address these issues in clinical practice.

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INTRODUCTION

Adolescence is a period during which individuals are subject to a high psychological burden and are often inclined toward depression and anxiety.[1,2] During this vulnerable time, the visibility of acne, atopic dermatitis (AD), and other appearance concerns can negatively affect self-image and relationships.[3-5] The magnitude of the mental health and psychosocial impact is proportional to acne or AD severity.[6,7]

Acne is a highly prevalent, chronic, inflammatory disease that affects approximately 80% of adolescents worldwide;[5,8-10] and is moderate to severe In 20% of cases.[11] Acne causes erythematous papulopustular lesions that often result in residual scarring and dyspigmentation[12,13] of the face, a highly visible area critical to self-esteem as well as social communication, occupational, and psychological functioning.[11,13,14] Unsurprisingly acne often

causes impairment of mental health, social functioning, and overall well-being.[13,14] Because acne is common, it is often trivialized and dismissed as being a cosmetic problem.[11,13] However, Its occurrence in adolescence adds significant psychological impact and comorbidity to the other emotional challenges commonly experienced in this age group.[9,12]

Atopic dermatitis is a common, relapsing, chronic inflammatory skin disease that affects up to 20% of children and adolescents [7,15]; approximately 20% of all cases are moderate to severe.[15] It presents with pruritus, pain, xerosis, and eczematous lesions.[16,17] The unpredictable disease course and signs/symptoms of AD, including itch, pain, and sleep disturbance can significantly impact an adolescent's mental health, potentially leading to depression, disrupted social functioning, and other impairments in quality of life (QoL).[2,16,17] Several studies have shown that the itch-scratch cycle in AD is the main cause of decreased health-related quality of life (HRQoL), as it may cause sleep deprivation, confidence issues, and stigmatization due to the appearance of the skin.[15,16,18]

The complex psychological, social, and physiologic landscape that adolescents experience may also cause a desire for cosmetic surgery.[3] Actual or perceived facial and body flaws can cause low self-esteem, psychological distress, and social isolation in adolescents.[19] The introduction of social media, unrealistic appearance ideals, appearance-based bullying and cyberbullying, and body shaming by peers have all contributed to a dramatic worldwide increase in teenagers seeking cosmetic procedures.[19,20] The American Society of Plastic Surgeons (ASPS) has reported that cosmetic procedures performed on adolescent patients in the US rose from 14,000 in 1996[21] to 229,740 in 2020.[22]

Challenges that adolescents face regarding their skin and body image require further examination. Though the contribution of psychological disorders to the burden of skin disease has been explored in adults through the nascent field of psychodermatology, psychological comorbidities have been underexplored in adolescent patients living with dermatologic conditions.[2,17] Many adolescent patients with acne or AD are undertreated, resulting in uncontrolled symptoms and a further strain on patients, caregivers, society, and the economy.[15,23] Rates of youth mental health conditions, including body image dissatisfaction, among adolescents with acne or AD are high, and mental health treatment utilization is low and often inaccessible.[23-26] Though many physicians recognize the need to address both the physical and psychological symptoms of their patients, they do not have clear guidelines on how to efficiently co-manage long-term psychosocial comorbidities in adolescent patients.[4,5,17] This review aims to provide insights into the psychosocial, occupational, and social media association with acne, AD, and self-image in adolescent patients.

METHODS

The project used a modified Delphi process comprising face-to-face discussions followed up online. A systematic literature search for the psychosocial, occupational, and social media association with acne, AD, and aesthetics in adolescent patients was performed by HA and AA from 14 to 16 January 2022. PubMed/Medline, Google Scholar, Cochrane Library, and PsycINFO were searched in the English language for publications from 01/01/2010 to 01/01/2022 on humans. The included article types comprised clinical studies (case-control, cohort, cross-sectional), consensus papers, meta-analyses, systematic reviews, and reviews. Search terms used AND OR for three groups (acne, AD, and esthetic procedures) (Table 1). First, the titles of 432 articles and abstracts were reviewed and after removing duplicates (excluding 282) 150 full articles were reviewed. After filtering for the English language, publication date, and suitability (excluding 28) for the subject at hand the searches yielded 122 publications (PubMed/Medline = 101, Google Scholar = 33, Cochrane Library = 2, and PsycINFO = 14 (Figure 1).

The systematic literature search results informed 14 draft statements. During the meeting, the draft statements underwent evaluation at the workshop by an expert panel of dermatologists, psychologists, and psychiatrists, followed by a plenary discussion. Five statements were adopted, using evidence from the literature coupled with the panel's opinions and experiences. The second step consisted of a post-meeting review of the manuscript by panel members.

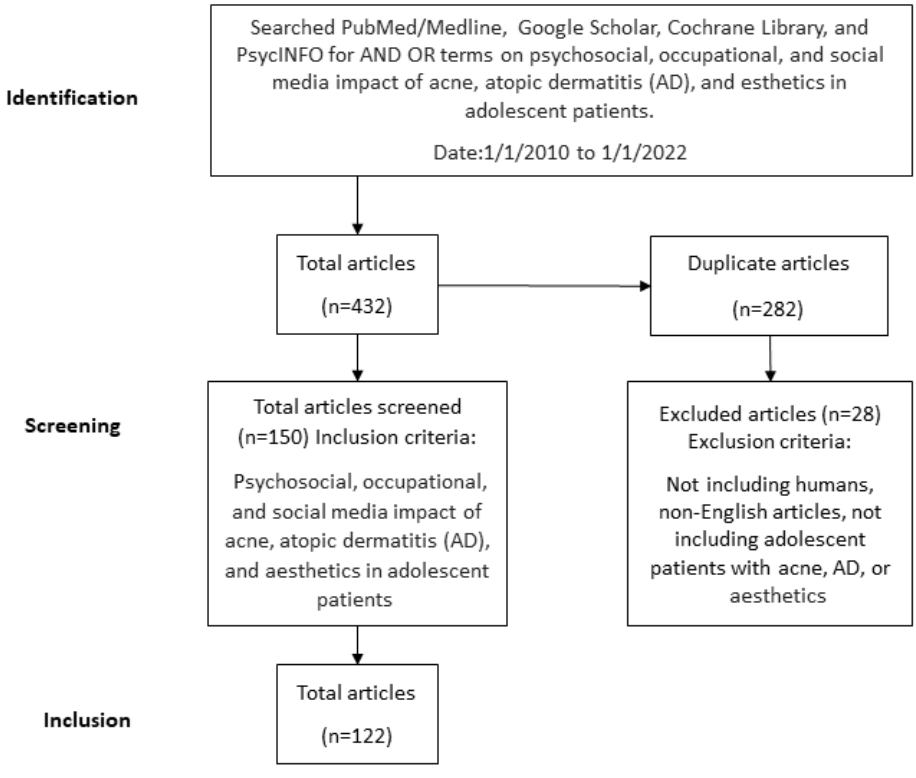
RESULTS AND DISCUSSION

Statement 1: *AD and acne are associated with an increased risk of poor sleep, social impairment, and mental health problems, including body image disturbance.*

Impaired sleep quality is one of the factors that is associated with the health of adolescents with acne or AD.[6,18] In a study by Tasoula et al sleeping disorders were identified in 20.3% of students with acne compared with 16.5% in the entire study population (P>.05).[6] The Children Dermatology Quality of Life Index scores for sleep disorders significantly correlated with acne severity (P<.0001). A study by Lim et al also found that a significantly higher percentage of students with acne had frequent insomnia compared with those without (11.6% vs 4.3%, P=.011).[27]

Sleep is reportedly disturbed in 60% of patients with AD.[28] A longitudinal study of 13,988 participants by Ramirez et al found that subjects with active AD had nearly 50% higher odds of experiencing more sleep-quality disturbances than those without AD.[29] In a study by Fishbein et al patients with AD had a higher frequency of daytime sleepiness (P<.01), difficulty falling back to sleep at night (P=.02), restless sleep (P=.01), and teacher-

FIGURE 1. Systematic literature search results.



reported daytime sleepiness (NS) than the control group.[28] Persistent AD with sleep disturbances has also been associated with a wide range of behavioral problems,[30] headaches,[31] and neurocognitive deficits in adolescents.[32]

Acne and AD are also associated with a broad range of mental and psychosocial disorders in adolescents, such as anxiety, depression, embarrassment, negative life events, BDD, psychosomatic symptoms, social inhibition, suicide, and suicidal ideation.[7,8,13,24,25,33] In a study by Kubota et al adolescent students with acne exhibited a significantly lower mean Mental Health Inventory (MHI) score (P<.01) and were significantly more depressed than those without acne (P<.01).[24] In a study by Halvorsen et al adolescent subjects with "very much" acne, compared with those with "no/little" acne, reported suicidal ideation 2 times more frequently among girls (25.5% vs 11.9%, P<.01) and 3 times more frequently among boys (22.6% vs 6.3%, P<.01).[34] Tasoula et al also identified a significant association (P <.0001) between impaired body image and severity of acne in children and adolescents.[6]

Numerous studies have identified psychological comorbidities in adolescent patients with AD. Kyung et al found that adolescent patients with AD experienced stress, depressive symptoms, and suicidal ideation at significantly (P<.001) greater rates (59.1%, 27.8%, and 13.9%, respectively), compared with those without AD.[25] Lee and Shin similarly found that adolescents with AD were significantly more likely (P<.001) to experience depression (OR 1.27, 95% CI 1.19-1.36) and suicidal ideation (OR 1.34, 95% CI 1.24-1.45), suicidal planning (OR 1.46, 95% CI 1.32-1.65), and suicide attempts (OR 1.51, 95% CI 1.33-1.72) compared with those without AD.[35] Khandaker et al also found that AD is associated with psychotic episodes (PE) in younger adolescents.[36] Compared with subjects without atopy, the risk of PEs at 13 y was increased for patients with AD (aOR, 1.33; 95% CI, 1.04–1.69) or both asthma and AD (aOR, 1.44; 95% CI, 1.06–1.94).

Acne and AD also affect psychosocial factors that contribute to self-esteem and identity development.[37,38] The results of a systematic review by Nguyen et al indicated that acne has a more direct effect on self-esteem, self-confidence, and identity, especially in girls, whereas AD has a more prominent role in the formation of identity and gender roles in girls and a lack of opportunity for the development of proper coping skills.[38] Moreover, the negative societal perception of skin diseases reinforces the psychological burden for adolescents with acne or AD.[30] Feelings of stigmatization are common and often associated with QoL impairment in patients with chronic skin diseases, such as acne, AD, and psoriasis.[1,4]

TABLE 1.

Search Terms Used for the Systematic Literature Review		
Group 1: Acne	**Group 2: Atopic dermatitis**	**Group 3: Esthetic procedures**
Acne AND	Atopic dermatitis AND	Esthetic procedure OR
adolescent AND	adolescent AND	cosmetic procedure OR
depress* OR	depress* OR	cosmetic surgery AND
anxi* OR	anxi* OR	nose reshaping OR
psychiat* OR	psychiat* OR	eyelid surgery OR
psycholog* OR	psycholog* OR	ear reshaping OR
psychosoc* OR	psychosoc* OR	laser hair removal OR
social media OR	social media OR	laser skin resurfacing OR
sleep OR	sleep OR	rhinoplasty OR
body dysmorphic disorder OR	body dysmorphic disorder OR	otoplasty OR
selective attention to perceived flaws	selective attention to perceived flaws	blepharoplasty AND
		adolescent AND
		depress* OR
		anxi* OR
		psychiat* OR
		psycholog* OR
		psychosoc* OR
		social media OR
		sleep OR
		body dysmorphic disorder OR
		selective attention to perceived flaws

Anxi, anxiety; depress, depression; psychiat, psychiatric; psycholog, psychologic; psychosoc, psychosocial.

Due to poor self-esteem and social phobia,[8] adolescents with acne often have difficulty socializing, making friends, meeting new people, interacting with the opposite sex, and fully participating in society.[6,39] The psychosocial and emotional impairment was found by Tasoula et al to be greater in adolescents with moderate/severe acne than in the general population ($P<.0001$).[6]

Hazarika et al identified a statistically significant correlation ($P<.05$) between acne grade and effect on work/studying; grade and site with embarrassment; site and post-acne pigmentation with interpersonal problems; grade with sexual difficulties; and grade and site with social activities.[12] In a study by Halvorsen et al a multivariate model similarly identified a negative association between substantial acne and psychosocial factors such as failure to achieve at school, low attachment to friendships, and absence of romantic relationships or sexual intercourse.[34]

Adolescents with AD have reported experiencing similar psychosocial challenges. In a study by Slattery et al adolescents with AD were found to have elevated rates of anxiety disorders (26%, 95% CI, 11.23-40.19%) compared with community estimates (3%–6%), with social anxiety disorder being most common (14%; 95% CI, 7.35-25.88%).[40] In a study by Muzzolon et al parents were more frequently concerned about socialization/bullying in children and adolescent subjects with AD compared with their siblings (33% vs 4%, $P<.001$).[41] Ghio et al identified three psychosocial needs in adolescents and young adults with AD: 1) the need to feel understood; 2) the need to blend in and be perceived as "normal"; and 3) the need for emotional support.[17] These needs reflect the emotions and behaviors of the subjects that were identified in this study, such as feeling low and anxious, socially isolating, hiding skin, and seeking support.

Statement 2: *Severe body image concerns, including BDD, present with high levels of psychological distress and are significantly associated with inflammatory skin diseases such as AD and acne.*

Adolescents with acne or AD, or those who desire cosmetic surgery, may present with BDD or body image concerns that resemble BDD.[42,43] Body dysmorphic disorder is a mental health disorder that involves distressing or impairing preoccupation

TABLE 2.

Study Summary
Summary of studies on the relationship between psychosocial and occupational factors, social media use, and mental health difficulties (BDD, suicidal ideation, depression, anxiety etc), and acne, atopic dermatitis (AD), and aesthetics in adolescents.

Author/year	N	What was studied	Key findings
Tan J, et al 2022[1]	724; 13-40 y	Cross-sectional, mixed methods, multinational CS using 60 min phone interview and online survey	• Based on SCORAD assessment, almost half of patients with AD who perceived they had severe disease, had moderate disease; these patients had higher DLQI, anxiety and depression scores
Tasoula E, et al 2012[6]	1531/11-19 y	Cross-sectional, questionnaire-based CS in 23 high school and senior high schools in Athens, Greece	• Sleep disorders more common in acne than in whole study population (20.5% vs 16.5%, *P*>.05) - Significant correlation between CDQLI scores for sleep disorders and acne severity (*P*<.0001) - Significant association (*P*<.0001) between impaired body image and acne severity - Psychosocial and emotional impairment greater in adolescents with moderate/severe acne (*P*<.0001
Yousaf A, et al 2020[10]	130/9-11 y (n=3); 12-18 y (n=70); >18 y (n=57)	Cross-sectional CS in West Virginia University Dermatology Clinic, Morgantown, WV, US	• 48% of adolescents and young adults adopt measures (eg, supplements or dietary changes) not supported by the AAD to treat acne due to advice on social media
Hazarika N, Archana M. 2016[12]	100/ >15 y (61% ≤ 20 y)	Prospective, cross-sectional CS in dermatology and STD outpatient clinic in tertiary care teaching hospital in India	• Significant correlation (*P*<.05) between acne grade and effect on work/study; grade and site with embarrassment; site and post-acne pigmentation with interpersonal problems; grade with sexual difficulties; and grade and site with social activities
Ghio D, et al 20211[7]	28/13-25 y	Cross-sectional CS using datasets from SKINS project and Eczema Care Online project, England, UK	• Emotions/behaviors (feeling low and anxious, social isolation, hiding skin, and seeking support) reflect 3 psychosocial needs identified in AD to: 1) feel understood; 2) blend in and be perceived as "normal"; 3) be emotionally supported
Desai KP, et al 2017[23]	Clinical sample: 120/13-18 y; Community sample: 482/ 11-18 y	Clinical sample: 120/13-18 y; Community sample: 482/ 11-18 y	• Clinical sample: self-reported increased acne severity (mild to moderate and mild to severe) raised the CADI score by 4.81 (*P*<.005) and 9.08 (*P*<.005), respectively* • Community sample: self-reported increased acne severity (mild to moderate and mild to severe) raised the CADI score by 1.92 (*P*<.001) and 7.41 (*P*<.005), respectively*
Kubota Y, et al 2010[24]	1443/13-19 y	Cross-sectional CS in 1 junior and 1 senior high school in Kagawa Prefecture, Japan	• Students with acne had a significantly lower mean MHI score (60.6 vs 68.5, *P*<.01) and were significantly more depressed (63.1 vs 71.2, *P*<.01) • Students with acne identified sweat (53%), stress (63.1%), and lack of sleep (55.5%) as the 3 most common factors that trigger or increase acne
Kyung Y, et al 2020[25]	62,276/12-18 y	Cross-sectional CS using 13th KYRBS Web-based Survey, South Korea	• Significantly (*P*<.001) greater rates of stress (59.1%), depressive symptoms (27.8%), and suicide ideation (13.9%) in AD
Lim TH, et al 2022[27]	582/16-25 y	Cross-sectional CS in 2 secondary schools and 2 universities, Sarawak, Malaysia	• Frequent insomnia more common in students with acne vs those without (11.6% vs 4.3%, *P*=.011)
Fishbein AB, et al 2018[28]	38/6-17 y	Case-control CS at Ann & Robert H. Lurie Children's Hospital of Chicago Allergy, Dermatology, or General Pediatrics Clinic, Chicago, IL, US	• Higher frequency of daytime sleepiness (*P*<.01), difficulty falling back to sleep at night (*P*=.02), restless sleep (*P*=.01), and teacher-reported daytime sleepiness (NS) in AD vs controls
Ramirez FD, et al 2019[29]	13988/2-16 y	Longitudinal cohort CS using Avon Longitudinal Study of Parents and Children birth cohort data, Avon, England, UK	• 50% higher odds of more sleep quality disturbances in AD (aOR, 1.48; 95% CI, 1.33 to 1.66)
Halvorsen JA, et al 2011[34]	3775/18-19 y	Cross-sectional, questionnaire-based CS in Youth 2004 Section, Oslo, Norway	• Suicide ideation 2x more frequent in girls (25.5% vs 11.9%, *P*<.01) and 3x in boys (22.6% vs 6.3%, *P*<.01) with "very much" vs those with "no/little" acne • Negative association between substantial acne and not thriving at school (OR 1.41; 95% CI, 1.12–1.78), low attachment to friendships (OR 1.52; 95% CI, 1.21–1.91), and never having a romantic relationship (OR 1.35; 95% CI, 1.05–1.70) or sexual intercourse (OR 1.51; 95% CI, 1.21–1.89)
Lee S, Shin A. 2017[35]	72,435/12-17 y	Cross-sectional CS using 9th KYRBS, South Korea	• Depression (OR 1.27, 95% CI 1.19-1.36) and suicide ideation (OR 1.34, 95% CI 1.24-1.45), planning (OR 1.46, 95% CI 1.32-1.65), and attempts (OR 1.51, 95% CI 1.33-1.72) significantly more likely (*P*<.001) in subjects with AD vs those without
Khandaker GM, et al 2014[36]	7814/10 y for AD diagnosis; 6785/13 y for PE evaluation	Population-based, longitudina cohort CS using ALSPAC and psychosis-like symptoms interview, Avon, England, UK	• PEs at 13 y increased for patients with AD (aOR, 1.33; 95% CI, 1.04–1.69) or both asthma and AD (aOR, 1.44; 95% CI, 1.06–1.94) vs no atopy

TABLE 2. (CONTINUED)

Study Summary
Summary of studies on the relationship between psychosocial and occupational factors, social media use, and mental health difficulties (BDD, suicidal ideation, depression, anxiety etc), and acne, atopic dermatitis (AD), and aesthetics in adolescents.

Author/year	N	What was studied	Key findings
Slattery MJ, et al 2011[40]	36/13-17 y	Cross-sectional pilot CS in dermatology and pediatric clinics, Wisconsin, US	• Elevated rates of anxiety disorders (26%, 95% CI, 11.23-40.19%) in AD vs community estimates (3%–6%); social anxiety disorder most common (14%; 95% CI, 7.35-25.88%) in AD
Muzzolon M, et al 2021[41]	150/1-18 y	Prospective, cross-sectional CS in tertiary hospital, Curitiba, Brazil	• Parents more frequently concerned about socialization/bullying for children/adolescents with AD vs siblings (33% vs 4%, *P*<.001)
Möllmann A, et al 2017[44]	308/15-21 y	Cross-sectional, questionnaire-based CS during Open House Day at the University of Munster, Germany	• Appearance-related suicidal ideation in significantly more subjects with self-reported BDD vs those without (36.4% vs 8.8%, *P*=.002)
Elsadek SM, et al 2021[46]	173/15-19 y	Cross-sectional, questionnaire-based CS in secondary school, Damietta Governate, Egypt	• Adolescents with acne experienced anxiety (82.7%), depression (76.9%), or BDD (46.8%)
Tavecchio S, et al 2020[49]	2327/12-21 y	Cross-sectional, questionnaire-based CS in University of Milan Dermatology Unit, Milan, Italy	• 65% of subjects were under treatment for acne; however, only 20% were consulting a dermatologist
Charmaraman L, et al 2021[51]	Body dissatisfaction subsample: 374/11-14 y	Cross-sectional, survey-based, pilot CS in ethnically and socioeconomically diverse middle schools with digital access in urban and suburban areas of the Northeast US	• 19% of subjects were dissatisfied with their body image • Most common concerns were not being sufficiently attractive (60%), not being thin enough (63%), or dissatisfied with hair/face (54%) or body shape (61%) • Subjects with social media-related body dissatisfaction vs those without checking their social media accounts more frequently (*P*=.024), were more socially isolated (*P*=.017), had a greater rate of depression (*P*= 000) and online social anxiety (*P*=.000), and found it challenging to make new friends (*P*=.002)
de Vries DA , et al 2014[52]	604/11-18 y	Longitudinal cohort CS using Netherlands Youth Institute and Rutgers WPF (Dutch Expert Centre on Sexuality) data, Netherlands	• Positive association between social media use, increased appearance investment (*P*<.001), and desire to undergo cosmetic surgery (*P*<.01)
Lyu Z, et al 2022[53]	537/14-20 y	Cross-sectional, questionnaire-based CS in 2 high schools, Henan, China	• Selfie behavior associated with a higher level of cosmetic surgery consideration (*P*<.001), which was mediated through upward comparison of facial appearance (*P*<.01)
Aktepe E, et al 2020[55]	186/14-18 y	Case-control CS in Dermatology Dept. of Süleyman Demirel University Medical Faculty Research and Practice Hospital, Isparta, Turkey	• Adolescents with acne more frequently overused (*P*=.022) and sought social benefit/comfort from the Internet (*P*=.041), were more exposed to its negative effects (*P*=.012), and more frequently participated in social media sites vs controls (*P*=0.044)

*Results according to gender-adjusted analysis.
AAD, American Academy of Dermatology; AD, atopic dermatitis; ALSPAC, Avon Longitudinal Study of Parents and Children; aOR, adjusted odds ratio; BDD, body dysmorphic disorder; CADI, Cardiff Acne Disability Index; CDLQI, Children Dermatology Life Quality Index; CI, confidence interval; CS, clinical study; DLQI, Dermatology Life Quality Index; KYRBS, Korean Youth Risk Behavior; MHI, Mental Health Inventory (MHI) subscale of the Short Form 36; NS, not significant; OR, odds ratio; PE, psychotic episode; SCORAD, sexually transmitted disease; UK, United Kingdom; US, United States; WV, West Virginia.

with perceived defects in physical appearance that appear only slight or non-existent to others.[42-44] A time-consuming obsessive focus on these perceived flaws can lead to many psychiatric comorbidities, social and occupational impairment, and a desire to have cosmetic surgery.[43] The results of a systematic review by Veale et al indicated that BDD is common, but poorly identified, in dermatology and cosmetic procedure settings.[45] This study found that the prevalence of BDD among adolescent and adult patients was 11.1% in acne dermatology clinics; 11.3% in medical dermatology outpatients; 9.2% in cosmetic dermatology outpatients; 13.2% in general cosmetic surgery patients; 20.1% in rhinoplasty surgery settings; and 11.2% in orthognathic surgery settings. However, cosmetic treatment (eg, dermatologic, surgical) virtually never improves BDD appearance concerns.

Body dysmorphic disorder most often develops in early adolescence. Although the causes of BDD are complex and multifactorial, and include genetic risk factors, negative social experiences, such as bullying, trauma and abuse during childhood may also be contributing factors.[21,43] An early age of onset increases the likelihood of developmental and psychological comorbidities and is associated with a higher rate of suicide attempts.[43,44] A study by Möllmann et al found that significantly more adolescents and young adults with self-reported BDD (36.4%) compared with those without BDD (8.8%) reported appearance-related suicidal ideation (*P*=.002).[44]

Anxiety, depression, and BDD have been found to occur more frequently among patients with acne, AD, and other inflammatory skin disorders compared with the general population.[33,46] In a study by Elsadek et al 82.7% of adolescent subjects with acne

experienced anxiety, 76.9% reported depression, and 46.8% had BDD.[46] Tasoula et al found that body image concerns have also been found to vary proportionately with self-reported acne severity ($P<.0001$).[6] Studies by Tan et al and Desai et al found that the scores of subjects who self-rated their acne as "severe" indicated greater psychological impairment on validated HRQOL scales.[1,23] A systematic review by Barlow et al found that in children and adolescents with chronic skin disorders, the prevalence of suicide attempts was 21.9% for subjects with acne and suicidal ideation occurred in 67% of subjects with BDD.[33] The odds ratio for suicide attempts was significantly increased for subjects with acne or AD.

Statement 3: *Education for patients with AD or acne and their parents leads to improved self-management skills and self-responsibility, better outcomes, improved quality of life for patients and caregivers, reduced treatment costs, and secondary prevention of comorbidities, including certain mental health disorders.*

Beliefs, misconceptions, and economic factors regarding acne are major challenges among cultures worldwide.[9,47,48] In addition many patients with acne don't readily seek help, so the disease is often undertreated.[9,23] Likewise many caregivers and patients with AD are also undereducated and undertreated, causing symptoms to often be uncontrolled, increasing stress on patients, caregivers, society, and the economy.[15]

Patients often have misconceptions regarding factors that exacerbate acne.[9] A study by Kubota et al found that the three most common factors that adolescent subjects thought triggered or increased their acne were sweat (53%), stress (63.1%), and lack of sleep (55.5%).[24] A study by Yousaf et al found that due to the high prevalence of acne treatment advice on social media, numerous adolescent and young adults (48%) adopted measures to treat acne (e.g. supplements or dietary changes) that aren't supported by the American Academy of Dermatology.[10] Instead of seeking treatment from a dermatologist, patients with acne also often seek other remedies.[9] Tavecchio et al determined that while 65% of the study subjects were under treatment for acne, only 20% were consulting a dermatologist.[49]

Early evidence-based educational interventions are critical to extinguishing myths and misinformation that may lead to acne or AD mismanagement, delayed access to healthcare, and psychological and/or physical scarring. A systematic review by Claudel et al concluded that identifying and attending to the concerns of young individuals with acne may improve the patient's sense of well-being as well as decrease emerging psychological comorbidities and related healthcare expenses.[47] Many investigators have suggested that educational programs should be established in high schools and colleges to ensure that adolescent students with acne are knowledgeable about their condition and are aware of available treatments. Such programs could improve mental health outcomes and prevent associated psychological disorders.[1,23,24,27]

Adolescents with AD would also benefit from education regarding their medical, mental, and psychosocial needs.[7] The German Atopic Dermatitis Intervention Study (GADIS) demonstrated that age-related educational programs for children and adolescents are effective in the long-term management of atopic dermatitis.[50] The economic burden of AD is also higher when the patient's condition is uncontrolled, highlighting the importance of education for patients and caregivers regarding disease control.[15]

Statement 4: *Teens look to social media for medical information and support when seeking cosmetic and dermatologic treatment; however, social media can contribute to unrealistic expectations and mental health conditions, including body image dissatisfaction.*

Social media has a powerful effect on frequent users of apps. The impact on adolescents may be more profound as they live in a period when physical and social comparisons, peer approval, and body self-consciousness influence self-worth.[21,51,52] Readily available smartphones and the widespread use of social media sites such as Instagram, TikTok, Twitter, SnapChat, and Facebook, have become integral to adolescent communication, entertainment, and information sharing about skin conditions.[21,53,54] Posting selfies that invite instant positive or negative feedback from one's peers is one of the most frequent activities that adolescents participate in on social media sites.[51,53]

Consequently, social media can foster self-objectification and unrealistic expectations that are based on current trends and idealized or manipulated images.[21,53] Participating in social media can cause adolescents to become obsessed with body image, depressed, isolated, and even suicidal.[21] It can worsen psychological comorbidities that may already exist secondary to acne or AD, increase body dissatisfaction, and encourage a desire for cosmetic procedures. Aktepe et al found that adolescents with acne more frequently overused ($P=.022$) the internet, more often sought social benefit/comfort from the internet ($P=.041$), and more frequently participated in social media sites ($P=0.044$), but were more exposed to negative effects ($P=.012$) compared with the control group.[55]

Social media has also been found to exacerbate the desire for cosmetic procedures in adolescents who are suffering from anxiety, depression, and low self-esteem.[21] In a study by Charmaraman et al, 19% of adolescent subjects reported dissatisfaction with their body image.[51] The most common concerns among participants were not being sufficiently attractive (60%) or thin (63%), and being dissatisfied with hair/face (54%) or body shape (61%). Subjects with social media-

related body dissatisfaction were more likely to check their social media accounts frequently than those without social media-related anxiety (*P*=.024). These individuals were also more socially isolated (*P*=.017), had a greater rate of depression (*P*=.000), and online social anxiety (*P*=.000), and found it challenging to make new friends (*P* =.002). Selfie behavior and social media use has also been found to enhance cosmetic surgery acceptance in adolescents.[52,53] Lyu et al investigated the relationship between selfie behavior, cosmetic surgery desire, social comparison, and concerns about facial appearance in a group of adolescents.[53] The results of this study showed that selfie behavior was associated with a higher level of cosmetic surgery consideration (*P*<.001), which was mediated through an upward comparison of facial appearance (*P*<.01).

Devries et al, in a longitudinal study, also identified that more social media use increased appearance investment (*P*<.001), and prospectively predicted a greater desire for cosmetic surgery (*P*<.01).[52]

Statement 5: *Social media use has potential benefits such as connection, support, increased self-esteem, safe identity experimentation, and an increased opportunity for self-disclosure. Body image acceptance and body positivity campaigns from social media platforms and social media-based micro-interventions may actively combat adverse outcomes in adolescent patients with AD or acne.*

Social media can benefit adolescents by providing a platform to seek emotional support, share experiences, and acquire information.[17,48] It also provides adolescents, including those with acne or AD, the opportunity to socialize while avoiding face-to-face interaction.[39] Social media and the Internet allow adolescents to independently access information; however, doing so makes them less reliant on more credible sources such as parents, teachers, doctors, therapists, and pharmacists.[48,56]

Exposure to the internet and social media-driven misinformation highlights the importance of educational interventions to increase education about acne and AD in adolescents. Improved health literacy has been associated with better health outcomes in numerous conditions, and it can be employed as a method to reduce negative outcomes.[48] The popularity of social media among adolescents makes it a powerful tool for advancing health literacy in this age group.[54] Healthcare professionals can create engaging videos about conditions like acne and AD to educate, entertain, and counteract misinformation that they may have been exposed to. Such videos can improve access to true experts, particularly for those adolescents who may not have the proximity or resources to seek in-person consultation. In addition, the increased use of social media for consultation and interaction between patients and healthcare professionals or hospitals may facilitate educational efforts.[10]

Educating adolescents with acne or AD about their disease and effective treatments is vital. Broad-based, long-term interventions that target adolescents and their families, peers, school environment, and community can also increase awareness, prevention, and treatment of mental health disorders.[57] Though most mental health services are still conducted in person, telehealth services are now widely available. Additional educational resources could soon be made available via low-cost digital interventions including websites and social media platforms established by healthcare providers, schools, and hospitals.[23] These resources could be used to connect adolescent patients with peers who have the same diagnosis, providing community and support to cope with their challenges.[4] Structured local and global informational campaigns could also be undertaken via the Internet and social networks.[47]

Physicians should be conscious to inquire about mental health and QoL impairment when treating adolescent patients with acne or AD and consider these issues when determining treatment.[15,23] A multidisciplinary approach to care and support should be taken, including educational programs for patients and families.[15] Patient needs, psychosocial factors, and education should be integrated into individual treatment and care plans to optimize patients' self-management capabilities. Support programs addressing stigmatization and other psychosocial effects of acne or AD in adolescents should be included in these plans.

CONCLUSION

Adolescents living with acne or AD may experience substantial health comorbidities, including adverse life events, depression, anxiety, suicidal ideation, and body image concerns. In seeking information about skin disease or body image, adolescents often consult the internet and social media. Exploring these avenues may have positive or negative aspects, at times providing helpful information, enhancing community, and reinforcing body positivity, at other times, offering misinformation, increasing social isolation, and worsening body image concerns. Educational programs for patients, families, and clinicians could increase awareness of the positive and negative aspects of social media use among adolescents and also help educate them about comorbid skin and psychological conditions. Action-oriented items should be created to assist dermatologists in addressing these issues in clinical practice, increasing mindfulness during patient examination, and promoting multidisciplinary discussion and outreach.

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CASE REPORT

Journal of Drugs in Dermatology

Verrucous Psoriasis: Rare Variant and Novel Treatment

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CASE

A 64-year-old female presented to the outpatient clinic for the evaluation of flaking and itchy lesions on her bilateral hands and feet that were present for several months and caused difficulty with activities of daily living. Inconsistent use of betamethasone and narrowband ultraviolet (UV)-B on the affected areas were both reported, neither of which improved the patient's symptoms. The physical exam was remarkable for yellow plaques with moderate scaling on over 50% of the patient's bilateral palmoplantar surfaces (see Figures 1, 3). The differential diagnosis included palmoplantar keratoderma, tinea pedis, and psoriasis. A fungal culture was performed from the patient's right plantar foot, but ultimately came back negative for growth after one month. Upon follow up at the one-month mark, a shave biopsy was performed on the right plantar surface to rule out psoriasis vs palmoplantar keratoderma.

FIGURE 1. Plantar surfaces: before.

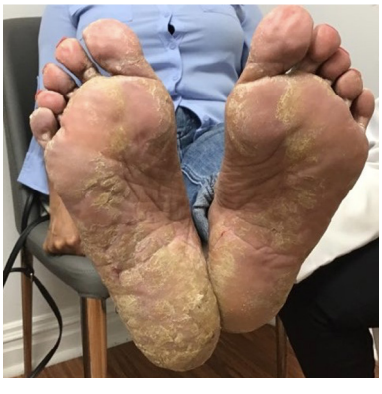


FIGURE 2. Plantar surfaces: after.

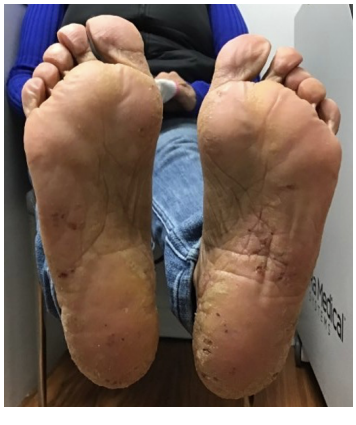
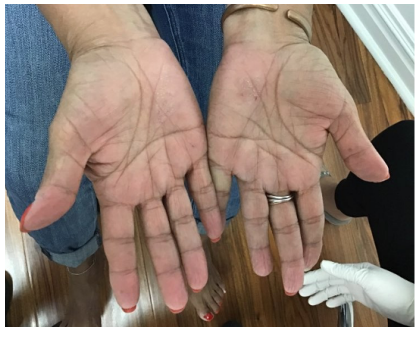


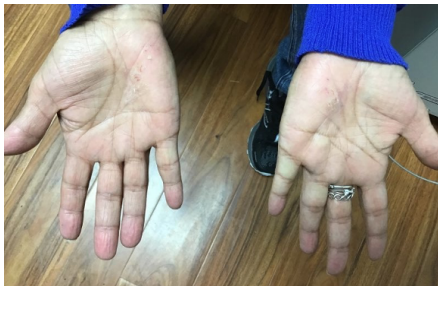
FIGURE 3. Palmar surfaces: before.



Histopathology revealed hyperkeratosis with neutrophils within mounds of parakeratosis, digitated and psoriasiform epidermal hyperplasia, dilated blood vessels at the tips of dermal papillae, and a superficial perivascular mixed inflammatory cell infiltrate. The condition was diagnosed as verrucous psoriasis (VP); since there is currently no standard treatment protocol for VP, the options of topical steroids, calcineurin inhibitors, vitamin D analogues, intralesional kenalog, and apremilast were considered. Ultimately, the decision to start apremilast was made; the patient started the 5-day titration schedule and went on to complete the 28 day starter pack.

Upon completion of the starter pack, the patient returned to the clinic for re-evaluation, at which time she denied side effects of depression or headaches, but admitted to mild gastrointestinal (GI) upset that self-resolved. Upon exam, the patient's lesions were reduced in size by approximately 50% on all surfaces and were lessened to mild in severity (Figures 2, 4). To our knowledge, this is the first time that apremilast has ever been used in the treatment of VP and we found that this novel approach significantly improved the patient's quality of life.

FIGURE 4. Palmar surfaces: after.



COMMENTARY

We had marked success with a novel approach for treating the rare and poorly understood condition of verrucous psoriasis by using apremilast.[2] In previous reports, patients were given kenalog and/or topical steroids with varying degrees of success.[3-6] Although upwards of 3 million cases of psoriasis are diagnosed annually in the US, verrucous psoriasis has only 20 reports currently in the literature.[1] Via this prototypical treatment with apremilast, we hope to shed some light on this otherwise not-well-understood and unusual histopathological variant of psoriasis.

DISCLOSURES

The authors have no conflicts of interest to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Talquetamab-Induced Grover's Disease

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INTRODUCTION

First reported in 1970, transient acantholytic dermatosis (TAD), also known as Grover disease (GD), is a rare transient dermatosis of largely unknown etiology.[1] It commonly occurs as grouped pruritic, papulovesicular skin eruptions on the trunk of men over the age of 40.[1] The histopathologic hallmark of the disease is acantholysis which is frequently accompanied by varying degrees of dyskeratosis and perivascular lymphohistiocytic infiltrate.[2,3] While the pathophysiology of disease is largely unknown, it has been reported to be associated with triggers such as heat, sweat, sunlight, medications, and neoplasms, specifically hematological malignancies.[4,5] GD also appears to be associated with states of immune modulation that occur in solid organ transplantation or in patients treated withinterleukin-4, cetuximab, vemurafenib, and ipilimumab.[6,7,8] GD is most often a self-limiting condition; however, because it can persist for long periods, it may be managed by high-potency topical corticosteroids, calcipotriol or a number of systemic agents including oral vitamin A, oral retinoids, systemic corticosteroids, TNF-alpha blocking biologics, PUVA or UVA-1.[9]

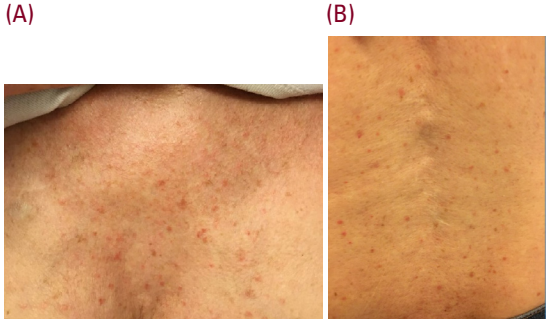
Talquetamab is a novel bispecific antibody currently under investigation, for use in refractory multiple myeloma (MM).[10] The novel antibody specifically targets MM cells via MM-specific target, GPRC5D, and simultaneously activates T-cell mediated killing via CD3 recruitment ofT cells. To date, the most common adverse events reported with the novel drug are cytokine release syndrome, neutropenia, and lymphopenia.

Here, we present a 74-year female with refractory multiple myeloma in treatment with talquetamab, who presents with persistent TAD.

CASE REPORT

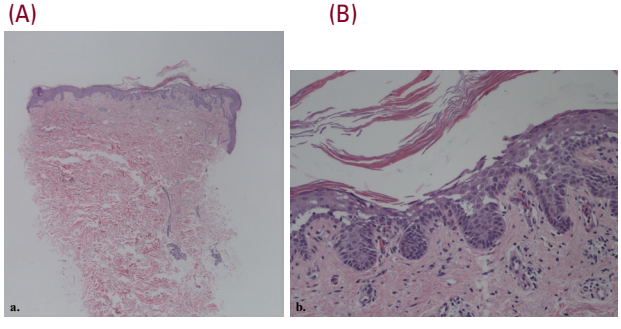
Our patient, a 74-year-old female with a past medical history of multiple myeloma, presented to our clinic with a 3-week history of a papular, non-pruritic rash on week 3 of biweekly talquetamab treatment (Figure 1A). The rash was predominately distributed across her chest and trunk with sparsely affected areas on her arms and legs (Figure 1B). There was no associated pain, burning, or itch in affected areas. Appearance of the rash was intermittent and occurred 2-3 days after each talquetamab treatment. As part of the trial protocol, the patient had received dexamethasone, an antihistamine, and an antipyretic prior to treatments with minimal relief of cutaneous symptoms. Other medications included atorvastatin and antacids.

FIGURE 1. Grover's Disease Induced by Talquetamab treatment in 74-year-old female. (A) Papular, non-pruritic rash on patient sternal chest. (B) Diffusely distributed papular rash on patient mid- and lumbar back.



After being seen in our office, the patient was given a trial of high-potency steroids betamethasone dipropionate and triamcinolone topical creams to apply on affected areas to treat a suspected drug reaction. The topicals provided minimal relief of symptoms and the patient returned to clinic shortly thereafter. At this time, a punch biopsy was performed and the diagnosis of transient acantholysis dermatosis, or Grover's disease was made (Figure 2).

FIGURE 2. Histopathologic studies of talquetamab-induced Grover's Disease. (A) Photomicrographs (H&E, 4x) shows section of a punch biopsy with focal acantholysis and dyskeratosis of the epidermis. (B) Photomicrographs (H&E, 20x) shows acantholytic epidermis with focal dyskeratosis.



In parallel, the patient's hematologist started concomitant use of IL-6 inhibitor, tocilizumab, and later switched to siltuximab. IL-6 inhibition appeared to reduce redness, dimension of lesion papules, and itch across affected areas albeit failing, to fully eliminate the rash. To date, the patient continues talquetamab treatment with promising results for her multiple myeloma.

DISCUSSION

Transient acantholysis dermatosis has been relatively poorly studied and understood. Most of our knowledge of this condition has stemmed from case reports and retrospective studies. Here, we present a case of GD following talquetamab treatment. This case may represent an immune-related adverse effect of the novel therapy. Indeed, GD has also been characterized as a paraneoplastic syndrome associated with hematologic malignancies such as multiple myeloma. Thus, the paraneoplastic explanation must not be discounted, nor can we rule out a coincidental occurrence of GD following talquetamab therapy.

However, the timing of our patient's lesions and improvement with use of IL-6 inhibitors that have been approved for autoimmune disorders suggest a possible immunologic effect of talquetamab.[11] IL-6 inhibitors down regulate auto-reactive cells such as Th2/Th17 cells while minimally affecting the tumor-killing Th1/CD8 cell axis.[11] Drawing from previous case reports demonstrating GD subsequent to ipilimumab treatment, it appears that GD may be a Th2-driven process. As talquetamab continues to be administered, the immune related adverse effect profile of the therapy will become more evident. As with other immune-modulatory therapies, there may be an increased risk for autoimmune adverse events as the immune system is harnessed for cancer destruction.

DISCLOSURES

Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica.

Authors Guénin, Kresch, Mubasher, and Elbogen have no conflicts of interest to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Juvenile Pemphigus Foliaceus in a Patient With Psoriasis Receiving Narrow-Band Ultraviolet-B: Successful Treatment With Rituximab

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ABSTRACT

Pemphigus foliaceus is an autoimmune blistering disease of the skin that is not frequently associated with mucous membrane involvement. It is characterized by immunoglobulin G (IgG) antibodies against desmoglein-1, a component of epidermal intercellular adhesion, in the granular layer of the epidermis. Pemphigus foliaceus consists of scattered, arcuate, crusted erythematous lesions often in a seborrheic distribution that may progress to diffuse skin involvement and exfoliative erythroderma. Several cases in the literature discuss pemphigus foliaceus arising in patients with pre-existing psoriatic disease following treatment with narrow-band ultraviolet-B (NB-UVB) therapy. Although this is a rare occurrence and the exact mechanism of this phenomenon remains unclear, providers should be aware of this association to better improve management and care. We present a case of a 16-year-old-male who developed pemphigus foliaceus following NB-UVB treatment for psoriasis.

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INTRODUCTION

There have been several case reports of pemphigus foliaceus arising in patients with psoriasis vulgaris treated with narrow-band ultraviolet B (NB-UVB) therapy.[1] It is thought that treatment with NB-UVB can trigger desmoglein autoantibodies in pemphigus foliaceus by damaging the dermal-epidermal junction.[2] Herein, we report a case of juvenile pemphigus foliaceus following NB-UVB therapy in a patient with a history of psoriasis vulgaris.

CASE REPORT

A 16-year-old male with no significant past medical history presented with a 14-month history of pruritic erythematous silver, scaly plaques on his scalp, face, chest, back, and legs sparing mucosal membranes with additional nail pitting. A family history of psoriasis was notable in his father and uncle. A skin biopsy was consistent with psoriasis vulgaris. After failing topical corticosteroid therapy, systemic treatment was initiated with ustekinumab with mild improvement in his psoriasis.

Ustekinumab was discontinued and secukinumab was initiated. However, he showed only slight improvement in his skin lesions following 3 months of secukinumab, which was discontinued. NB-UVB therapy was added for 11 cycles, but he began to progress to erythroderma with diffuse and generalized painful arcuate and polycyclic plaques with excoriations and scaling, and a few blisters that ruptured leaving superficial erosions (Figure 1). No mucosal lesions or joint pains were present. NB-UVB therapy was discontinued, and he was started on prednisone 60 mg daily. A repeat skin biopsy demonstrated an intracorneal split and direct immunofluorescence showed granular immunoglobulin G (IgG) deposition consistent with pemphigus foliaceus. Additionally, his blood was positive for anti-desmoglein-1 antibodies. Considering the adverse effects of

FIGURE 1. (A-D) Erythematous polycyclic and arcuate plaques with excoriations and scaling on the bilateral arms, chest, face, legs, and back.

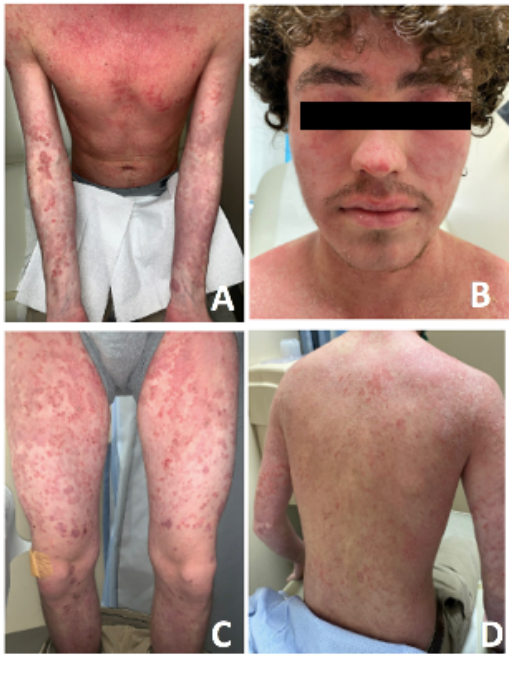
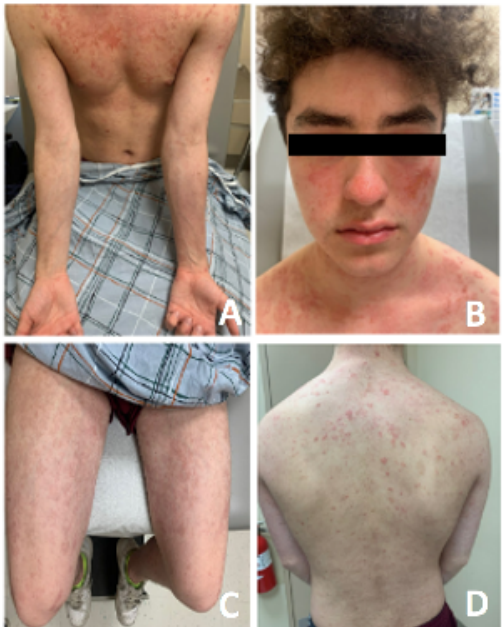


FIGURE 2. (A-D) Improvement in clearance of skin lesions following one infusion (1000 mg) of rituximab.



prolonged use of systemic corticosteroids, rituximab infusions were initiated at doses of 1000 mg 2 weeks apart. Following his first infusion, the patient had significant improvement in his skin lesions with less pronounced erythema and experienced no new lesions (Figure 2). Oral prednisone was decreased to 40 mg. Following his second infusion, there was marked improvement in his lesions.

DISCUSSION

Based on the patient's clinical and histopathological results from his second biopsy, a diagnosis of pemphigus foliaceus was made. Pemphigus foliaceus is a rare autoimmune blistering disease of the skin with little or no mucous membrane involvement.[3] It is characterized by the presence of an autoantibody to desmoglein-1, a cell adhesion molecule, causing acantholysis in the epidermal granular layer.[1] Clinically, pemphigus foliaceus causes superficial flaccid vesicles and bullae with well-demarcated arcuate and/or polycyclic scaly, crusted erosions on an erythematous base.[3] Although the mechanism of pemphigus foliaceus arising in a patient with psoriasis receiving NB-UVB is unknown, both diseases may be genetically associated with one another since an increased incidence of human leukocyte antigen DRB1 has been observed in both diseases.[1]

Although rare, there have been a few reports in the literature discussing pemphigus foliaceus developing in pre-existing psoriatic disease potentially provoked by NB-UVB therapy. The pathogenesis of this phenomenon is not well understood. However, it is hypothesized that the NB-UVB can damage the dermal-epidermal junction and provoke acantholysis and the production of desmoglein autoantibodies that target the epidermal intercellular spaces.[4] NB-UVB irradiation may cause injury to the skin, thereby exposing desmoglein antigens and facilitating an immune response. Additionally, autoreactive lymphocytes in psoriasis patients may cause further autoimmune reactions and epidermal stimulation of autoantibodies.[1]

Although uncommon, patients with psoriasis treated with narrow-band UVB may be at an increased risk of developing pemphigus foliaceus. Clinicians need to keep this diagnosis in mind when a patient experiences a similar disease and treatment course.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Rethinking the Inflammatory Balance in Psoriasis and Atherosclerosis

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INTRODUCTION

Psoriasis and atherosclerosis have largely been understood as inflammatory diseases. While these two diseases have complex pathophysiologies, they both appear to be mixed Th1/Th17 cell-driven and tied together through the "psoriatic march". Broadly, the psoriatic march establishes a causal link between psoriasis and cardiovascular comorbidity through systemic inflammation and activation of inflammatory pathways that lead to insulin resistance, alterations in angiogenesis, endothelial dysfunction, and subsequent increased risk for atherosclerosis and future myocardial infarction (MI). The inflammatory link between psoriasis and cardiovascular disease may have important clinical implications.

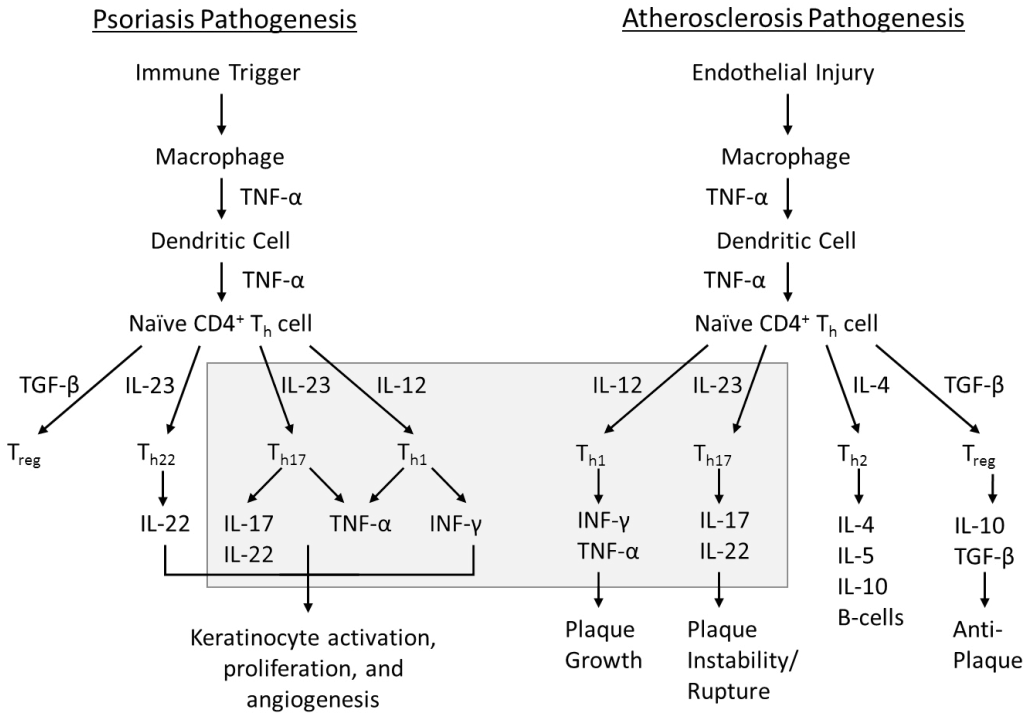
Consistent with the proposed shared pathophysiology, psoriasis is an independent risk factor for atherosclerotic heart disease (Figure 1). In 1978, McDonald and Calabresi linked psoriasis to an increased risk of arterial and venous vascular disease. Almost 30 years later, Gelfand et al. investigated psoriasis as an independent risk factor for MI, and the relative risk of MI was elevated most in young patients with severe forms of psoriasis. In other studies, psoriasis was not found to be an independent risk factor. The association may be confounded by the high rate of metabolic syndrome and obesity associated with psoriasis. Thus, it may be difficult to distinguish psoriasis from metabolic syndrome as an etiology of acute coronary syndrome. In addition, psoriasis drugs such as methotrexate, systemic retinoids, and cyclosporine have atherogenic effects. For example, cyclosporine can induce or worsen arterial hypertension and alter lipid metabolism, while retinoids may increase triglyceride levels.

The effect of psoriasis treatment on cardiovascular morbidity is not clear. In a systematic review investigating the impact of biological agents on cardiovascular disease in patients with psoriasis, there were no significant reductions in biomarkers of cardiovascular disease in patients treated with adalimumab or secukinumab compared to placebo. Adalimumab caused a strong reduction in CRP, TNF-α, IL-6, and GlycA without a decrease in aortic vascular inflammation.[1] In other studies, TNF-α inhibitors had neutral or reductive effects in cardiovascular disease.[2,3] Contradictory results may be explained by opposing signaling events triggered by TNF-α. TNF-α activates both TNFR1 and TNFR2, which lead to both cardiac disease and protection, respectively. TNF-α levels are increased in heart failure and contribute to atherogenesis, inflammatory gene induction, and vascular dysfunction. However, TNFR2 activation may activate the SAFE pathway which signals via JAK/STAT3 and leads to cardioprotective effects through the regulation of oxidative stress.[4] This may be evidenced by worsened heart failure with infliximab treatment.[5]

Cytokines may need to be rebalanced to reduce cardiovascular risk. Based on in vitro and in vivo studies, cytokines such as interleukin (IL)-17, have both pro-atherogenic and anti-atherogenic effects. IL-17 inhibition reduces psoriatic lesions; however, its effects on atherosclerosis is less clear. IL-17a-null mice have reduced atherosclerosis, and IL-17a blockade in ApoE-deficient mice reduces atherosclerosis, suggesting that IL-17 has pro-atherogenic effects.[6,7] Further, IL-17 increases production of pro-atherogenic IL-6, TNF-α and monocyte recruitment. In contrast, IL-17 blockade in human studies appears to have a neutral effect on atherosclerosis burden, implying that IL-17 may also have anti-atherogenic effects. This may be due to IL-17's protective effects on vascular plaque stability via stimulation of collagen type I production by smooth muscle cells. Thus, instead of adopting a global anti-inflammatory approach to reducing cardiovascular risk in psoriasis patients, it may be more useful to envision a fine balance of IL-17 to stabilize existing atherosclerotic plaques while concomitantly reducing the formation of new ones.

Given the opposing effects of many psoriasis-related cytokines in the pathogenesis of atherosclerosis, a non-dichotomous framework for cardiovascular risk reduction in psoriasis may be needed. To date, canakinumab, an IL-1ß inhibitor, is the

FIGURE 1. Psoriasis and aortic inflammation.



Convergence of pathophysiology of psoriasis and atherosclerosis.

only immune-modulating biologic that reduces cardiovascular events independent of lipid reduction. Thus, instead of a general reduction in inflammation, we should strive to identify how inflammation should be modulated to reduce cardiovascular risk. A deeper understanding of the clinical implications of cytokine balance in psoriasis and cardiovascular disease is critical to target and reduce potential morbidity and mortality in these patients.

DISCLOSURES

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Journal of Drugs in Dermatology

No Racial Differences Found in Access to Biologics: A Population-Based Study of Psoriasis Patients in the United States

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ABSTRACT

Background: Conflicting evidence exists regarding the role of race in access to biologics for patients with psoriasis.
Objective: To compare biologic use among adult and pediatric United States psoriasis patients of different racial backgrounds.
Methods: Population-based study of US psoriasis patients using the 2003 to 2018 Medical Expenditure Panel Survey (MEPS).
Results: Among 31,525,500 adults and children with psoriasis (weighted), 3,026,578 (9.6%) were on biologics. Among psoriasis patients, 27,464,864 (87.1%) self-identified as white, 2,033,802 (6.5%) self-identified as Black, 1,173,435 (3.7%) self-identified as Asian or Pacific Islander, and 853,399 (2.7%) self-identified as other races. Among those on biologics, 2,778,239 (91.8%) self-identified as white, 84,971 (2.8%) identified as Black, 89,452 (3.0%) self-identified as Asian or Pacific Islander, and 73,917 (2.4%) self-identified as other races. Multivariate logistic regression revealed no significant differences in biologic access between whites and non-whites after adjusting for sociodemographic factors including insurance status (OR for Blacks: 0.347 [0.118, 1.021], *P*=0.055; OR for Asians: 0.616 [0.240, 1.579], *P*=0.311; OR for other races: 0.850 [0.216, 3.336], *P*=0.814.
Conclusion: The results of this study suggest that race alone is not independently associated with access to biologics among adult US psoriasis patients. Additional studies are necessary to evaluate factors independently associated with biologics access among adults and children with psoriasis in the US.

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INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects more than 7.5 million people in the United States.[1] Although psoriasis is most prevalent in whites (3.2%), African Americans often exhibit more extensive skin involvement, present with more severe variants of psoriasis, and experience greater psychological burden and impaired quality-of-life than whites.[2-6] Since 2003, biologics have become increasingly popular for the treatment of moderate-to-severe psoriasis, and have resulted in higher patient satisfaction and compliance rates compared with oral, photo, or topical therapies.[7,8] However, multiple studies have shown that African Americans have less access to biologics than whites.[9,10] A 2015 study on the US Medicare population demonstrated that African American patients were 69% less likely to use biologics compared with white patients.[11] However, the association between race and biologics has not been evaluated in a nationally representative psoriasis population. This population-based study aims to evaluate the impact of race on access to biologics among adult and pediatric psoriasis patients in the US. We hypothesized that our analysis would demonstrate racial differences in biologics access similar to previous studies.

We conducted a cross-sectional, population-based study using the Medical Expenditure Panel Survey (MEPS) national database from 2003-2018. We identified adults and children (mean age 49.36 years) with a reported diagnosis of psoriasis by the ICD-9 diagnosis code "696" or ICD-10 code "L40". Race was categorized based on the MEPS classification: white, Black, Asian or Pacific Islander, Alaska Native or American Indian, or multiple races; the latter two groups were later grouped together due to insufficient sample size. Access to an approved biologic medication for psoriasis was identified by the household-reported receipt of a prescription biologic. Multivariate logistic regression was used to investigate the association between race and access to biologics, adjusting for potential confounders including age, sex, ethnicity, insurance status, education level, poverty level, personal income, employment status, number of outpatient visits, region of care, and the Charlson Comorbidity Index.

A weighted total of 31,525,500 adult and child patients with psoriasis in the US were identified from 2003 to 2018. 87.1% self-identified as white, 6.5% self-identified as Black, 3.7% self-identified as Asian, and 2.7% self-identified as other races,

including Alaska Native, Native American, and multiple races. Among all psoriasis patients, 3,026,578 (9.6%) were prescribed biologics. Among those who received biologics, 2,778,239 (91.8%) identified as white, 84,971 (2.8%) identified as Black, 89,452 (3.0%) identified as Asian, and 73,917 (2.4%) identified as other races. The adjusted multivariate regression analysis revealed no racial differences in biologics access compared with whites (OR for Blacks: 0.347 [0.118, 1.021], *P*=0.055; OR for Asians: 0.616 [0.240, 1.579], *P*=0.311; OR for other races: 0.850 [0.216, 3.336], *P*=0.814; Table 1).

TABLE 1.

Multivariate Logistic Regression Analysis of the Association Between Race and Psoriasis Adjusting for Comorbidities and Covariates *P<0.05

Independent Variables	Dependent Variable: Prescription of bilogical medication (weighted n = 3,026,578)	
	Odds Ratio (95%)	*P*-Value
Race		
Black vs. White[a]	0.347 [0.118, 1.021]	0.055
Asian, Native American, or Pacific Islander vs. White[a]	0.616 [0.240, 1.579]	0.311
Other Race vs. White[a]	0.850 [0.216, 3.336]	0.814
Age	0.986 [0.970, 1.002]	0.081
Sex		
Female vs. Male[a]	0.746 [0.469, 1.187]	0.215
Ethnicity		
Hispanic vs. Non-Hispanic[a]	0.391 [0.141, 1.085]	0.071
Poverty Level Category		
Near poor vs. Poor[a]	1.721 [0.628, 4.718]	0.29
Low income vs. Poor[a]	1.745 [0.646, 4.715]	0.271
Middle income vs. Poor[a]	1.425 [0.575, 3.529]	0.442
High income vs. Poor[a]	1.109 [0.452, 2.717]	0.821
Insurance Status		
Public vs. Private[a]	0.951 [0.471, 1.919]	0.887
Uninsured vs. Private[a]	0.209 [0.040, 1.092]	0.063
Marital Status		
Married vs. Not Married[a]	1.458 [0.850, 2.502]	0.17
Employment Status		
Employed vs. Unemployed[a]	2.135 [1.291, 3.531]	0.003*
Highest Education Level		
High School vs. Lower[a]	3.799 [1.365, 10.575]	0.011*
Some College/Degree vs. Lower[a]	2.019 [0.720, 5.663]	0.181
Region of Residence		
Midwest vs. Northeast[a]	0.980 [0.517, 1.856]	0.95
South vs. Northeast[a]	1.250 [0.736, 2.122]	0.407
West vs. Northeast[a]	1.061 [0.513, 2.194]	0.872
Charlson comorbidity index	1.129 [0.844, 1.510]	0.411
Number of ambulatory visits for psoriasis	1.012 [0.994, 1.030]	0.192

Our study revealed no significant association between race and biologic access among US psoriasis patients. Our results differ from our *a priori* hypothesis and previous studies that demonstrated certain races were less likely to receive biologics for treatment of their psoriasis.[9,11] The differences in findings between this study and previous findings might be attributable, at least in part, to the patient populations. This study uses Medical Expenditure Panel Survey (MEPS), which draws on a nationally representative sample of adult and pediatric patients over a 15-year time span. We also adjusted for possible contributory factors including ethnicity, insurance status, and poverty level with no significant differences found across all racial groups.

Biologics remain one of the most effective treatment options for psoriasis. While access to biologics does not appear to be significantly different between white and non-white racial groups, racial minorities experience more severe psoriasis and psychological burden than their white counterparts. This may lead to delayed diagnosis and subsequent more severe disease on initial presentation.[2,5,6,12] Barriers to seeking dermatologist care for psoriasis among non-whites may include lack of cultural competency and low density of dermatology providers in areas where significant proportions of people of color reside.[13,14] Socioeconomic and demographic factors, other than race, such as older age, poor English language proficiency, and lower income level, may also exacerbate access to biologics, and thus result in more severe disease.[8,15] Further investigation is needed to elucidate potential additional demographic, socioeconomic, and clinical risk factors contributing to increased disease severity faced by minority patients.

DISCLOSURES

April W. Armstrong MD MPH has served as a research investigator and/or scientific advisor to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed. All remaining authors have no disclosures.

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LETTERS TO THE EDITOR

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The Patient-Physician Relationship and Adherence: Observations From a Clinical Study

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ABSTRACT

Improved patient-physician relationships (PPR) are associated with better patient satisfaction and disease outcomes, however, there is limited literature assessing how PPR affects adherence in dermatology. We recruited 30 subjects with a clinical diagnosis of rosacea. Subjects were instructed to use ivermectin 1% cream once daily for 3 months and adherence was measured using the Medication Event Monitoring System cap. The Patient-Doctor Relationship Questionnaire (PDRQ-9), a validated questionnaire assessing patients' perceived strength of the relationship with their doctor, was completed. Mean adherence for all subjects over three months of the study was 62%. PDRQ-9 scores positively correlated with adherence rates for 3 months of treatment ($r(26)=0.52$; $P=0.006$). The perceived strength of the PPR may have a role in patients' adherence to their medications. Improving the PPR, through empathy and effective communication, may facilitate better medication adherence and treatment outcomes.

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INTRODUCTION

Adherence in dermatology can be very poor, particularly with topical medications and complex treatment regimens.[1] Improved patient-physician relationships (PPR) are generally associated with better patient satisfaction, disease outcomes, and also adherence.[2] However, there is limited literature assessing how PPR affects adherence in dermatology.[3] We assessed how patient-reported PPR affects adherence in a clinical study of patients with rosacea.

MATERIALS AND METHODS

After Institutional Board Review approval (IRB00062694), 30 subjects with a clinical diagnosis of rosacea were recruited from the Atrium Health Wake Forest Baptist Department of Dermatology clinics. Subjects were instructed to use ivermectin 1% cream once daily for 3 months with visits at baseline and 3-month follow-up. The Medication Event Monitoring System (MEMS®), a cap with an electronic device that records the time and date of cap removal, was used to measure adherence over a 3-month period.[4] Subjects were not informed about the adherence monitoring until the end of study. The Patient-Doctor Relationship Questionnaire (PDRQ-9), a validated questionnaire assessing patients' perceived strength of the relationship with their doctor, was completed at the follow-up visit (Table 1).[3] The PDRQ-9 consists of 9 questions, each graded on a 1-5 Likert scale (1 = not at all appropriate, 2 = somewhat appropriate, 3 = appropriate, 4 = mostly appropriate, 5 = totally appropriate), with a range of 9 to 45; higher scores indicate greater strength of PPR (Table 1). Three subjects were excluded (two lost to follow-up and one failure to follow protocol). Data were stratified based on PDRQ-9 scores of ≤ 36 and ≥ 37, age < 50 and ≥ 50, and gender. Differences in group comparisons were analyzed with Student's t-test and correlation between PDRQ-9 and adherence

TABLE 1.

Mean Patient-Doctor Relationship Questionnaire (PDRQ-9) Score by Question and Total Score for Low PDRQ-9 (≤ 36) and High PDRQ-9 Groups (≥ 37)

	Low PDRQ-9 Group Mean (n=10)	High PDRQ-9 Group Mean (n=17)
My physician helps me	3.4	4.9
My physician has enough time for me	3.4	4.8
I trust my physician	3.4	4.9
My physician understands me	3.2	4.8
My physician is dedicated to help me	3.6	4.8
My physician and I agree on the nature of my medical symptoms	3.1	4.7
I can talk to my physician	3.6	4.9
I feel content with my physician's treatment	3.4	4.8
I find my physician easily accessible	3.3	4.8
Total PDRQ-9 Score	**30.4**	**43.4**

TABLE 2.

Mean Adherence by Age, Gender, and Patient-Doctor Relationship Questionnaire (PDRQ-9) Score for Subjects With Rosacea Receiving Ivermectin Cream 1%					
Mean adherence for < 50 years old (n=13)	Mean adherence for ≥ 50 years old (n=14)	Mean adherence for females (n=19)	Mean adherence for male (n=8)	Mean adherence for PDRQ-9 ≥ 37 (n=17)	Mean adherence for PDRQ-9 ≤ 36 (n=10)
64%	58%	59%	66%	70%	45%

was assessed using a univariate linear regression model. Data was analyzed using the SAS Software 9.4.

RESULTS

Subjects were mean age 62 years (median 50 years), 93% Caucasian, and 70% female. Mean adherence for all subjects over three months of study was 62% (median 66%). Mean PDRQ-9 score for all subjects was 38.5 (median 40). Subjects who perceived a weaker PPR (≤ 36, n=10) were less adherent over 3 months, with an average adherence rate of 45%, compared with subjects who perceived a stronger PPR (≥ 37, n=17), with an average adherence rate of 70% (P=0.03). PDRQ-9 scores positively correlated with adherence rates for 3 months of treatment (r(26)=0.52; P=0.006). Adherence did not vary by age or gender (P=0.59 and 0.51, respectively; Table 2).

DISCUSSION

Subjects with a stronger perceived PPR had greater adherence over three months of treatment. The perceived strength of the PPR may have a role in patients' adherence to their medications. Improving the PPR, through empathy and effective communication, may facilitate better medication adherence and treatment outcomes.[5]

DISCLOSURES

Dr. Feldman has received research, speaking, and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Baxter, Boeringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Taro, Abbvie, Cosmederm, Anacor, Astellas, Janssen, Lilly, Merck, Merz, Novartis, Regeneron, Sanofi, Novan, Parion, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Patrick Perche, Rohan Singh, Madison Cook, Katherine Kelly, Esther Balogh, and Irma Richardson have no conflicts of interest to report.

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Antimalarials Are Not Effective as Pre-Exposure Prophylaxis for COVID-19: A Retrospective Matched Control Study

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ABSTRACT

The early phase of the COVID-19 pandemic prompted a repurposing of antiviral and immunomodulatory drugs as investigational therapeutics, including hydroxychloroquine and chloroquine. While antimalarials have been well-refuted as a treatment for COVID-19, data on these drugs' role in preventing SARS-CoV-2 infection as pre-exposure prophylaxis is more limited. We investigated the efficacy of antimalarial drugs as pre-exposure SARS-CoV-2 prophylaxis in a US tertiary-care center. We identified all adult patients exposed to antimalarials with active prescriptions from July 1, 2019 to February 29, 2020 and exact-matched antimalarial-treated study patients with controls on age, sex, race, and Charleston Comorbidity Index. We used multivariable logistic regression to calculate the odds ratio (OR) of COVID-19 diagnosis by antimalarial exposure, adjusting for demographics, comorbidities, local infection rates, and specific conditions identified in early studies as risk factors for COVID-19. There were 3,074 patients with antimalarial prescriptions and 58,955 matched controls. Hydroxychloroquine represented 98.8% of antimalarial prescriptions. There were 51 (1.7%) infections among antimalarial-exposed and 973 (1.6%) among controls. No protective effect for SARS-CoV-2 infection was demonstrated among antimalarial-exposed patients in the multivariate model (OR=1.06, 95% CI 0.80-1.40, *P*=0.70). These findings corroborate prior work demonstrating that hydroxychloroquine and related antimalarials do not have a role in protection against SARS-CoV-2.

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To the Editor:

The early phase of the COVID-19 pandemic prompted a repurposing of antiviral and immunomodulatory drugs as investigational therapeutics, including hydroxychloroquine and chloroquine.[1] Despite an early interest in these potentially preventative medications given positive in vitro findings,[2] randomized control trials of hydroxychloroquine as post-exposure prophylaxis did not reveal differences in infection susceptibility; appropriately, antimalarials are not recommended for treatment of COVID-19.[3]

While antimalarials have been well-refuted as a treatment for COVID-19, data on these drugs' role in preventing SARS-CoV-2 infection as pre-exposure prophylaxis is more limited. Hydroxychloroquine is frequently prescribed for dermatologic and rheumatologic diseases, and thus data on this drug's pre-exposure impact on SARS-CoV-2 risk is of great importance to the practicing dermatologist. We investigated the efficacy of antimalarial drugs as pre-exposure SARS-CoV-2 prophylaxis in a US tertiary-care center.

MATERIALS AND METHODS

We included all adult patients with at least one prescription for chloroquine, hydroxychloroquine, or quinacrine from July 1, 2019 to February 29, 2020 (limiting prescriptions to those started before the pandemic onset) in the MassGeneral Brigham Enterprise Data Warehouse and Research Patient Data Registry. We exact-matched antimalarial-treated study patients with controls on age, sex, race, and Charleston Comorbidity Index. Additional collected variables included zip codes (used to estimate income using 2010 US Census), and medical history using ICD-9/ICD-10

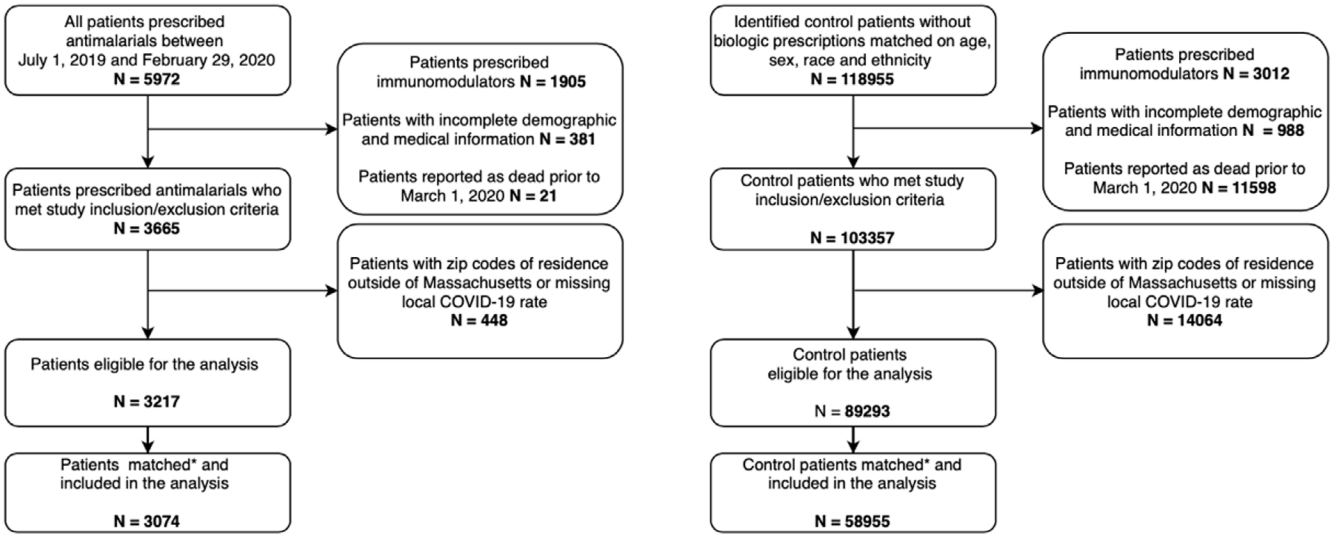
TABLE 1.

Multivariable Logistic Regression of the Risk of SARS-CoV-2 (COVID-19) PCR Test Positivity

	Antimalarials Group N = 3074	Matched Control Group N = 58955	*P*-value	OR	95% CI	*P*-value
Age group N (%)	--	--	1.00	--	--	--
18-44	718 (23.4%)	13770 (23.4%)	--	ref*	ref*	ref*
45-64	1272 (41.4%)	24395 (41.4%)	--	0.92	0.76 – 1.11	0.38
65-74	637 (20.7%)	12217 (20.7%)	--	0.54	0.42 – 0.70	< 0.001
≥75	447 (14.5%)	8573 (14.5%)	--	0.90	0.69 – 1.16	0.42
Female sex N (%)	2611 (84.9%)	50075 (84.9%)	1.00	1.20	1.01 – 1.43	0.04
Race and ethnicity N (%)	--	--	1.00	--	--	--
White Non-Hispanic	47678 (80.9%)	2486 (80.9%)	--	ref*	ref*	ref*
Asian/PI Non-Hispanic	2033 (3.4%)	106 (3.4%)	--	0.69	0.45 – 1.07	0.10
Black Non-Hispanic	4296 (7.3%)	224 (7.3%)	--	1.52	1.25 – 1.84	< 0.001
Other Non-Hispanic	2033 (3.4%)	106 (3.4%)	--	1.27	0.96 – 1.68	0.10
Hispanic	1285 (2.2%)	67 (2.2%)	--	0.78	0.50 – 1.22	0.27
Unknown	1630 (2.8%)	85 (2.8%)	--	0.65	0.38 – 1.12	0.12
CCI grade N (%)	--	--	1.00	--	--	--
Mild (1-2)	1275 (41.5%)	24453 (41.5%)	--	ref*	ref*	ref*
Moderate (3-4)	799 (26.0%)	15324 (26.0%)	--	1.12	0.92 – 1.38	0.26
Severe (≥5)	1000 (32.5%)	19179 (32.5%)	--	1.90	1.48 – 2.45	< 0.001
Comorbidity N (%)						
Hypertension	1130 (36.8%)	20308 (34.4%)	< 0.01	1.41	1.21 – 1.63	< 0.001
Congestive heart failure	231 (7.5%)	4771 (8.1%)	0.25	1.75	1.47 – 2.09	< 0.001
Diabetes mellitus	382 (12.4%)	11376 (19.3%)	< 0.001	1.15	0.99 – 1.34	0.07
COPD	499 (16.2%)	11622 (19.7%)	< 0.001	1.23	1.06 – 1.42	0.01
Other chronic pulmonary disease	729 (23.7%)	18089 (30.7%)	< 0.001	0.94	0.82 – 1.07	0.34
Renal disease	310 (10.1%)	6069 (10.3%)	0.71	1.23	1.03 – 1.47	0.02
Liver disease	416 (13.5%)	11344 (19.2%)	< 0.001	0.93	0.80 – 1.09	0.38
Hematologic cancer	122 (4.0%)	2601 (4.4%)	0.24	0.62	0.44 – 0.87	0.01
Solid organ cancer	499 (16.2%)	15953 (27.1%)	< 0.001	0.87	0.74 – 1.02	0.10
Metastatic cancer	81 (2.6%)	3643 (6.2%)	< 0.001	0.59	0.43 – 0.83	< 0.01
Inflammatory bowel disease	76 (2.5%)	1617 (2.7%)	0.37	0.70	0.46 – 1.06	0.09
Rheumatic disease	1939 (63.1%)	3768 (6.4%)	< 0.001	0.79	0.62 – 0.99	0.05
Socio-geographic factors	3 (5.8%)	83 (8.5%)	0.53	--	-	--
County SARS-CoV-2 PCR test positivity rate per 100 Mean (SD)	1.46 (0.91)	1.59 (1.11)	< 0.001	1.24	1.19 – 1.30	< 0.001
Median income ($1,000x) Mean (SD)	81.7 (2.9)	79.3 (2.9)	< 0.001	0.99	0.96 – 1.01	0.38
COVID-19 positive N (%)	51 (1.7%)	973 (1.6%)	0.97	N/A	-	--
Died N (% of PCR-positive patients)	3 (5.8%)	83 (8.5%)	0.53	N/A	--	--

Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; OR = odds ratio; PCR = polymerase chain reaction; PI = Pacific Islander; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; and SD = standard deviation.

FIGURE 1. Study flow diagram for selection of antimalarials-exposed cases and matched controls.



*Patients treated with antimalarials were matched with controls using exact matching on age, gender, race, and age adjusted numerical Charleston Comorbidity Index (CCI) score.

Abbreviations: COVID-19 = coronavirus disease 2019

codes. Massachusetts Department of Public Health and COVID-19 Dashboard provided data on COVID-19 diagnosis status, and baseline county rates, respectively. Patients with incomplete data, non-Massachusetts zip codes, and prescriptions for other immunomodulator drugs were excluded (see Supplemental Table at https://data.mendeley.com/datasets/5z2vdhzbs4/1). We used multivariable logistic regression to calculate the odds ratio (OR) of COVID-19 diagnosis by antimalarial exposure, adjusting for demographics, comorbidities, local infection rates, and specific conditions identified in early studies as risk factors for COVID-19.[4,5] Pearson's chi-square and two-tailed t-tests were used for pairwise comparisons of categorical and continuous variables, respectively.

RESULTS

There were 3,074 patients with antimalarial prescriptions and 58,955 matched controls (Figure 1). Hydroxychloroquine represented 98.8% of antimalarial prescriptions (Table 1). There were 51 (1.7%) infections among antimalarial-exposed and 973 (1.6%) among controls. No protective effect for SARS-CoV-2 infection was demonstrated among antimalarial-exposed patients in the multivariate model (OR=1.06, 95% CI 0.80-1.40, *P*=0.70).

Ages 65-74 were less likely to have confirmed COVID-19 diagnosis than patients aged 18-44 years (OR=0.61 [0.48-0.79], *P*<0.001). Sex did not affect susceptibility (OR=1.05 [0.88-1.24], *P*=0.61). Black patients had a higher infection risk than white patients (OR=1.64 [1.35-1.98], *P*<0.001). Severe comorbidity burden also increased SARS-CoV-2 infection risk (OR=2.32 [1.92-2.81], *P*<0.001). Local infection rates predicted SARS-CoV-2 infection (OR=1.26 [1.21-1.32], *P*<0.001), while median income by zip code did not (OR=0.98 [0.96-1.01], *P*=0.18).

Among the comorbidities analyzed, hypertension (OR=1.41 [1.21-1.63], *P*<0.001), congestive heart failure (OR 1.75 [1.47-2.09], *P*<0.001), COPD (OR=1.23 [1.06-1.42], *P*=0.01), and renal disease (OR=1.23 [1.03-1.47], *P*=0.02) were identified as independent risk factors for COVID-19. Hematologic cancer (OR=0.62 [0.44-0.87], *P*=0.01), metastatic cancer (OR=0.59 [0.43-0.83], *P*<0.01), and rheumatic disease (OR=0.79 [0.62-0.99], *P*=0.05) were found to have a protective effect.

DISCUSSION

We found that pre-pandemic antimalarial prescriptions were not protective of COVID-19 diagnosis among queried individuals, consistent with past evidence demonstrating these agents' lack of efficacy as post-exposure prophylaxis.[3]

Antimalarials are frequently used to manage chronic cutaneous and systemic autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, and juvenile idiopathic arthritis.[6] Interestingly, we identified that a history of rheumatic disease – as well as hematologic cancer or metastatic cancer – was

independently significantly associated with a lower risk for SARS-CoV-2 infection. Given that the treatment of rheumatic disease and hematologic/metastatic malignancy – with systemic immunosuppression and chemotherapy, respectively – can plausibly reduce the immune response to SARS-CoV-2, patients with a history of these diseases may engage in protective behaviors to limit their potential exposure to infection, as has been reported amongst patients with rheumatic diseases.[7,8]

Limitations include Massachusetts-restricted data and a single-center perspective. Study patients who were prescribed antimalarials were more likely to live in zip codes with lower COVID-19 incidence rates and higher average incomes, which may be confounded by differential access to care.

Antimalarial agents – particularly hydroxychloroquine – received significant consideration as a potential treatment for or prophylactic drug against COVID-19.[2] We demonstrate that, amongst patients with antimalarial prescriptions predating the COVID-19 pandemic in Massachusetts, antimalarials did not significantly prevent SARS-CoV-2 infection. These findings corroborate that hydroxychloroquine and related antimalarials do not have a role in protection against SARS-CoV-2.

DISCLOSURES

The authors above have no conflicts of interest to disclose for the following work.

IRB approval status: This study was approved by the Institutional Review Boards at Mass General Brigham (Protocol 2020P001191) and Massachusetts Department of Public Health (Protocol 1606024-2).

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FEATURED CONTENT

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NEWS, VIEWS, & REVIEWS

EXTRA, EXTRA, Treatment Approaches for EXTRAmammary Paget Disease

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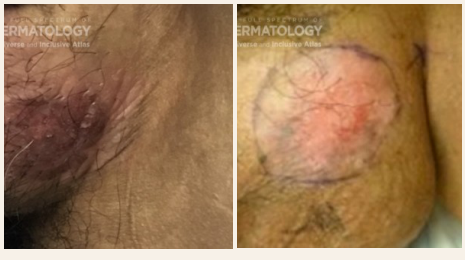
Introduction

Extramammary Paget Disease (EMPD) is a rare intraepithelial malignancy of pluripotent keratinocyte stem cells that presents on apocrine-rich skin of the perineum, vulva, and less commonly, axilla.[1] EMPD clinically presents as a slow growing, unilateral, strawberry-pink scaly patch or plaque, frequently impacting Caucasian women in their sixth to eight decades (Figure 1).[1,2]

Figure 1. Extramammary Paget Disease of the perineum and breast.[10]



While typically confined to the epidermis, EPDM can be invasive, associated with contiguous extension or upward pagetoid spread of underlying neoplasms or with distant synchronous malignancy.[3] The complexity of EMPD intertwined with the heterogeneity of the disease in its appearance, location, and depth of invasion, often requires a multidisciplinary approach to management (Table 1).[1]

There have been recent significant developments in further characterizing EMPD, such as identification of associated mutations in TP53, ERBB, NRAS, BRAF, PIK3CA, and AKT1 genes and overexpression of P16 protein and the HER2 and Androgen Receptor (AR) signaling pathways.[2] However, given EMPD is a rare disease, there are no established guidelines regarding diagnosis and treatment modalities.[2,3,4] Herein we review evidence and provide insight for non-surgical and surgical approaches utilized for EMPD.

Non-surgical Management

EMPD often elicits inherent surgical limitations due to its aggressive nature, ill-defined margins, and subclinical extension; therefore, conservative treatment approaches are ideal.[5,6]

Imiquimod

As a toll-like receptor 7 agonist, imiquimod induces innate and cell-mediated inflammatory responses and subsequent cell apoptosis.[2,3] Imiquimod can be used as monotherapy, adjunctive therapy before or after surgery, as well as part of a therapeutic combination with other management modalities. Complete remission (CR) when used as a single agent ranged from 52% to 72%, according to one study.[2,3] Eighty-five percent of patients experienced greater than 50% clinical regression; unfortunately,

Table 1. Treating Extramammary Paget Disease[2-8, 15,16,17]

Management	Modality	Best Clinical Use
I. ***Non-surgical Approaches***	Topical [eg, Imiquimod, 5-FU, Bleomycin]	Not well-established and limited evidence of its overall efficacy; high rates of recurrence and often toxic s/e
	Photodynamic Therapy	EMPD lesions of < 4 cm
	Radiation Therapy [Dosing: 10 Gy to 64 Gy]	Primary EMPD or adjuvant setting
	Holium Laser	EMPD limited to the dermis and epidermis areas
	Carbon Dioxide Laser	EMPD limited to the dermis and epidermis areas
II. ***Surgical Approaches***	Wide Local Excision [1 cm incision margins]	Well-defined EMPD lesions only
	Mohs Micrographic Surgery	1st line: primary excision or for recurrences from wide local excision
	Sentinel Lymph Node Biopsy	In cases where regional metastasis is present
III. ***Systemic Therapy***	Combination Chemotherapy of Low-Dose FP and Cisplatin	Advanced EMPD cases
	FECOM Therapy	Metastatic EMPD
	HER-2 Therapy	Deep invasion and lymph node metastasis as well as aggressive EMPD cases
	Trastuzumab	Metastatic EMPD
	Docetaxel + S-1	Metastatic EMPD
	Trastuzumab + Paclitaxel	Metastatic EMPD

40% of individuals with CR had disease recurrence, thus highlighting the importance of continued follow-up.[2]

5-Fluouracil (5-FU)

Topical 5-FU is a pyrimidine analogue that acts by inhibiting synthesis of DNA and RNA.[2] Despite being utilized as field therapy for actinic keratoses and topical treatment for both superficial basal cell carcinoma and squamous cell carcinoma in situ, its efficacy for EMPD is limited. One case series studied its application in combination with 0.005% calcipotriene twice daily for a twelve-week duration on patients with refractory EMPD. Although clinical lesions cleared, biopsy specimens following the treatment course showed persistent disease with no patient achieving CR.[2,8]

Photodynamic Therapy (PDT)

Patients undergoing PDT are exposed to photoreactive agents which are selectively taken up by tumor cells, and then exposed to appropriate wavelengths of light creating reactive oxygen species that allows selective destruction of neoplastic tissue.2[7] Multiple EMPD case reports revealed antitumor responses to PDT with one systematic review showing a complete response rate of 46.2% and recurrence rate of 33.6% to PDT alone. Overall results indicate that PDT can be beneficial when used as a palliative treatment to minimize EMPD associated symptoms.[2,3,6]

Radiation Therapy

Radiation therapy may be used as a first-line treatment in patients with inoperative primary EMPD, recurrent EMPD, as well as adjuvant therapy after surgery.[2] In one retrospective study, all primary EMPD tumors treated with radiation resolved by 2-to-9 months, yielding a 100% initial CR rate. Twenty-one percent of patients developed local recurrence after a median follow-up of 41 months, and local progression-free survival rates were 78% at 3 years and 69% at 5 years.[3] Another study found post-surgical radiotherapy with a median total dose of 59.4Gy achieved 100% local control after a median follow-up of 38 months and 55% attained progression-free survival at 5-year follow-up.[2,7,8] Furthermore, radiation is also routinely used to treat lymph node metastases, although minimal evidence of its efficacy exists.[2]

Surgical Management

Surgical excision remains the cornerstone treatment of choice for non-invasive EMPD, whether via wide local excision (WLE) with margins of 2-to-5cm or Mohs micrographic surgery (MMS), especially when definitive clearance is possible but can be limited by irregularities of borders, leading to positive margins, unresected satellite lesions, and high rates of local recurrence. Studies demonstrate that a clinically determined border of well-defined EMPD neoplasms permit adequate WLE with 1-cm surgical margins, whereas 2-cm margins are appropriate for ill-defined EMPD lesions.

There is growing evidence that MMS presents favorable patient outcomes with improved relapse-free survival (RFS) and recurrence rates of EMPD when compared to WLE.[2,7,8] MMS allows complete frozen section analyses of excised tumors, maximizing normal tissue conservation while optimizing cure rates.[3,11,12] Results from one retrospective study uncovered an estimated 5-year RFS rate of 91% versus 66% and an estimated 5-year overall survival rate of 79% versus 68% with MMS versus WLE, respectively.[4] Positive margins were reported in 3.4% patients after MMS compared to 33.3% of patients who underwent WLE.[4] A second study found a 37.4% recurrence rate of EMPD after non-MMS surgical excision versus 1.6% with MMS.[4,5]

Conclusion

Every case of EMPD is morphologically unique; the rarity of the disease and research to date supports that management varies vastly and evidence-based approaches are lacking. Future global collaborations with supportive groups can be imperative in designing EMPD clinical trials and effective database evaluation in hopes of establishing foundational EMPD practice guidelines and treatment interventions.[2]

Disclosure

The authors declare no conflicts of interest.

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PIPELINE PREVIEWS

US FDA Review of The Biologics License Application for Bimekizumab

UCB, a global biopharmaceutical company, today announced that the Biologics License Application (BLA) for bimekizumab for the treatment of adults with moderate to severe plaque psoriasis remains under review with the United States (US) Food & Drug Administration (FDA). UCB previously communicated the FDA action was expected in Q2, 2023. UCB now anticipates the FDA action in Q3, 2023. There are no open Information Requests from the FDA regarding the BLA for bimekizumab.

UCB is committed to ongoing collaboration with the FDA to bring bimekizumab to people in the US living with moderate to severe plaque psoriasis as soon as possible.

Bimekizumab, an IL-17A and IL-17F inhibitor, is currently approved for moderate to severe psoriasis by 10 regulatory authorities and in 39 countries worldwide.[1-8] In June 2023, in countries of the European Union/European Economic Area, bimekizumab was approved for two additional indications – the treatment of adults with active psoriatic arthritis, and for the treatment of adults with active axial spondyloarthritis (axSpA), including non-radiographic axSpA and ankylosing spondylitis, also known as radiographic axSpA.[2]

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