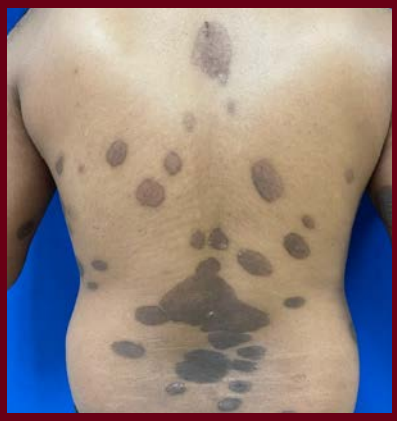
ISSN: 1545 9616

March 2024 • Volume 23 • Issue 3

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS



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Head-to-head superiority for full body relief[1]

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NMFs=natural moisturizing factors.

Reference: 1. Data on file. Beiersdorf Inc.

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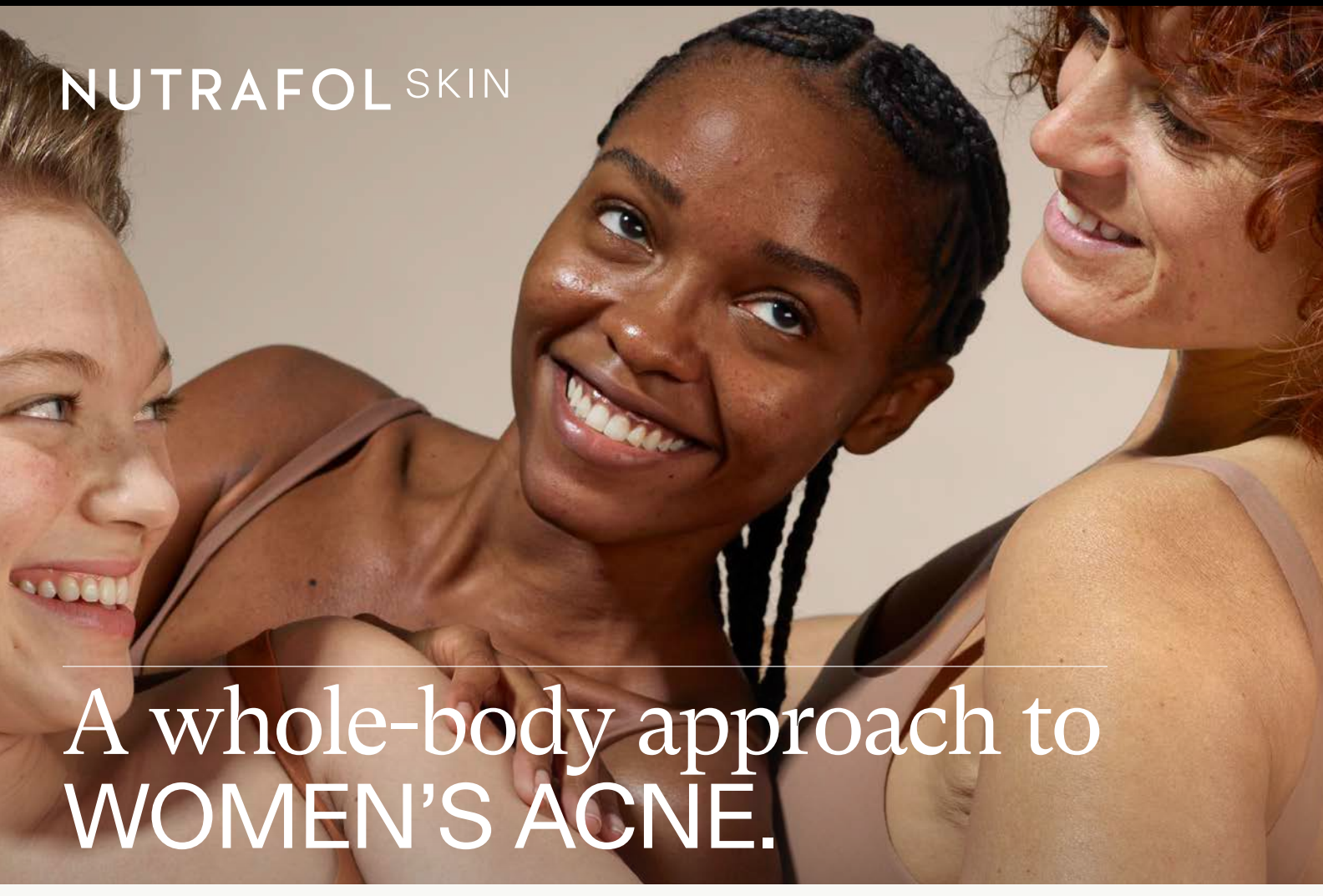

A whole-body approach to WOMEN'S ACNE.

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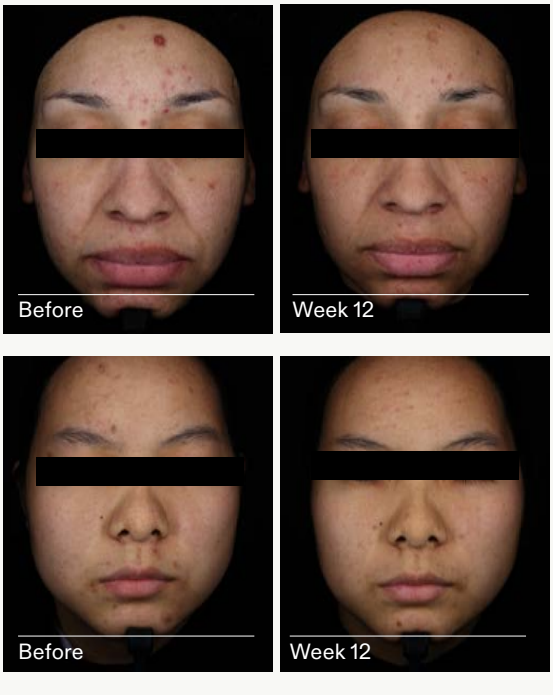

In a 12-week clinical study evaluating the efficacy of Nutrafol Clear Skin Nutraceutical in subjects with non-cystic acne (ages 18-50)[1]:

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These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

*According to IQVIA ProVoice survey for 12 months ending March 31, 2023.

1. Raymond I, et al. SKIN: J Cutan Med. 2024./Nutrafol. Data on file. 2023.

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Journal of Drugs in Dermatology (JDD) (ISSN 1545-9616) is published monthly for $300 per year US Individual subscriptions/$350 per year International Individual subscriptions/(Corporate and Institutional rates contact Sales for a quote) by the *SanovaWorks*, c/o WebMD, 283 - 299 Market St, 2 Gateway Center, 4th Floor, Newark, NJ 07102. Periodicals postage paid at New York, NY and additional mailing offices.

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POSTMASTER: Send address changes to the Journal of Drugs in Dermatology,
PO Box 2008, Cedar Rapids IA 52406-2008

Journal of Drugs in Dermatology (JDD)
is indexed in MEDLINE®/PubMed® and is published monthly by the
***SanovaWorks*, c/o WebMD**
283 - 299 Market St, 2 Gateway Center, 4th Floor, Newark, NJ 07102
telephone: 212-213-5434 | JDDonline.com

doi:10.36849/JDD.7907

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Early and Sustained Acne Lesion Reductions With Fixed-Dose Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel

Julie C. Harper MD,[a] Leon Kircik MD,[b] Michael Gold MD,[c] Adelaide A. Hebert MD,[d] Jeffrey L. Sugarman MD PhD,[e] Lawrence Green MD,[f] Linda Stein Gold MD,[g] Hilary Baldwin MD,[h] Eric Guenin PharmD PhD MPH,[i] James Del Rosso DO[j]

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[c]Tennessee Clinical Research Center, Nashville, TN; [d]UTHealth McGovern Medical School Houston, Houston, TX; [e]University of California, San Francisco, CA; [f]George Washington University School of Medicine, Washington, DC; [g]Henry Ford Hospital, Detroit, MI; [h]The Acne Treatment and Research Center, Brooklyn, NY; [i]Ortho Dermatologics, Bridgewater, NJ;* [j]JDR Dermatology Research/Thomas Dermatology, Las Vegas, NV; Advanced Dermatology and Cosmetic Surgery, Maitland, FL; Touro University Nevada, Henderson, NV

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

ABSTRACT

Background: A once-daily, three-pronged approach using an antibiotic, antibacterial, and retinoid may provide faster acne improvement versus monotherapy or dual-combination products. This post hoc analysis compared threshold acne lesion reductions with clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel—the first FDA-approved triple-combination topical acne product—to its dyads and vehicle.

Methods: Phase 2 (N=741; NCT03170388) and phase 3 (N=183; N=180; NCT04214639; NCT04214652), double-blind, 12-week studies randomized participants aged ≥9 years with moderate-to-severe acne to once-daily CAB or vehicle gel; the phase 2 study included three additional dyad gel arms. The pooled percentage of participants achieving ≥33%, ≥50%, and ≥75% reduction in inflammatory and noninflammatory acne lesions was evaluated.

Results: As early as week 4 in the phase 2 study, ≥33% reduction in inflammatory lesions occurred in a significantly greater percentage of CAB gel-treated participants (82.7%) than with the 3 dyads and vehicle (61.1-69.8%; $P<0.05$, all). These early reductions were sustained throughout the study, with significantly ($P<0.05$) more CAB-treated participants achieving ≥50% reduction in inflammatory lesions versus dyads and vehicle from weeks 4-12. By week 12, CAB led to substantial reductions of ≥75% in significantly more participants than dyads and vehicle (65.8% vs 49.9-51.2% and 21.6%; $P<0.05$, all). Similar trends were observed for noninflammatory lesions in the phase 2 study and for inflammatory and noninflammatory lesions in the phase 3 studies.

Conclusions: Lesion count reductions were significantly greater with CAB versus its dyads and vehicle gel as early as week 4, with substantial reductions observed after 12 weeks of treatment. This faster-acting and sustained efficacy of CAB gel—coupled with its optimized formulation, once-daily dosing, and tolerability—may positively impact treatment adherence.

J Drugs Dermatol. 2024;23(3):125-131. doi:10.36849/JDD.7907

INTRODUCTION

Acne vulgaris is a common dermatologic condition that can have a profound psychosocial impact on patients' quality of life.[1,2] While several oral and topical drugs are currently available for acne therapy, treatment can be challenging owing to the chronic nature of acne and its multifactorial underlying pathology.[1] Treatment is further hindered by low adherence typical of acne therapies,[3-6] with multiple factors contributing to nonadherence including side effects, difficulty incorporating the treatment routine, and treatment cost.[7] Additionally, many acne medication regimens currently available may take weeks or months to produce an improvement discernible by patients. This lag between treatment initiation and acne improvement noticeable to patients can further reduce adherence, potentially contributing to treatment failure.[1,8]

Combination therapies that simultaneously target multiple processes of acne pathogenesis are recommended in the US for the majority of patients with acne.[9] A three-pronged combination approach using once-daily application of an antibiotic, antibacterial agent, and retinoid may provide faster improvement than stand alone or dual combination products. The first triple-combination, fixed-dose acne treatment approved by the US Food and Drug Administration, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide (BPO) 3.1% (CAB; Cabtreo™; Ortho Dermatologics) gel, has been evaluated in three 12-week studies of participants with moderate-to-severe acne.[10,11] In a phase 2 study, once-daily CAB was well tolerated and demonstrated efficacy that was significantly superior to vehicle and three dyad combinations of the active ingredients.[10] Two identical randomized, phase 3, double-blind, vehicle-controlled trials confirmed the efficacy, safety, and tolerability of CAB.[11] Further, the onset of action with CAB was rapid: percent reductions from baseline in acne lesions were significantly greater with CAB than vehicle gel as early as week 2 in the phase 2 study (both inflammatory and noninflammatory lesions, $P<0.05$, both)[10] and phase 3 studies (inflammatory lesions only; $P<0.05$ all).[12] This is important as treatments associated with fast and substantial or complete clearance of acne lesions are highly desirable to patients with acne[13] and can promote treatment adherence.[6]

While the literature on what is considered "acne improvement" by patients is scarce, one analysis of data from >4,000 patients suggests that a 10-15% reduction in acne lesions is relevant to patients.[14] Using data from three clinical studies of CAB gel, the objective of this post hoc analysis was to determine the percentage of participants meeting threshold reductions of inflammatory and noninflammatory acne lesions of at least 33%, 50%, and 75% following treatment with CAB gel compared to its three dyads (BPO/adapalene, clindamycin phosphate/BPO, and clindamycin phosphate/adapalene) and vehicle gel.

MATERIALS AND METHODS

Study Design and Participants

These analyses included data from a phase 2 (NCT03170388) and two phase 3 (NCT04214639; NCT04214652), double-blind, 12-week studies.[10,11] Eligible participants were aged ≥9 years with moderate-to-severe acne (a score of 3 or 4 on the Evaluator's Global Severity Score [EGSS]). Eligible participants also needed to have the following facial lesions: ≥30 to ≤100 inflammatory (pustules, papules, and nodules), ≥35 to ≤150 noninflammatory (closed and open comedones), and two or fewer nodules. Participants were randomized either 1:1 (phase 2 study) or 2:1 (phase 3 studies) to receive once-daily clindamycin phosphate 1.2%/adapalene 0.15% gel/BPO 3.1% (CAB) or vehicle gel; the phase 2 study included three additional dyad gel randomization arms: BPO 3.1%/adapalene 0.15%; clindamycin phosphate 1.2% /BPO 3.1%; and clindamycin phosphate 1.2%/adapalene 0.15%. For optimal moisturization, cleaning, and protection of the skin, CeraVe® hydrating cleanser, CeraVe® moisturizing lotion (L'Oreal, New York, NY), and sunscreen were provided as needed.

Studies were carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. At all investigational sites, the study protocol was approved by the relevant independent ethics committees or institutional review boards. All participants or their legal guardians provided written informed consent.

Study Assessments and Post Hoc Statistical Analyses

For each study, efficacy evaluations included least-squares mean percent change from baseline in inflammatory and noninflammatory lesion counts. Assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12 (treatment end). Data from the phase 3 studies were pooled prior to analysis. When significant skewness was observed for lesion counts, a nonparametric method was used in which data were rank transformed prior to an analysis of covariance, with factors of treatment group and analysis center and covariate of baseline lesion count. Lesion counts at weeks without significant skewness were based on non-rank-transformed data. For all efficacy assessments, multiple imputation was used to impute missing values using the Markov Chain Monte Carlo method.

For this post hoc analysis, the percentage of participants achieving ≥33%, ≥50%, and ≥75% thresholds in lesion reduction were evaluated at baseline and each assessment week for the phase 2 and pooled phase 3 studies. All statistical analyses were performed using SAS® version 9.3 or later. Statistical significance was set at $P<0.05$.

RESULTS

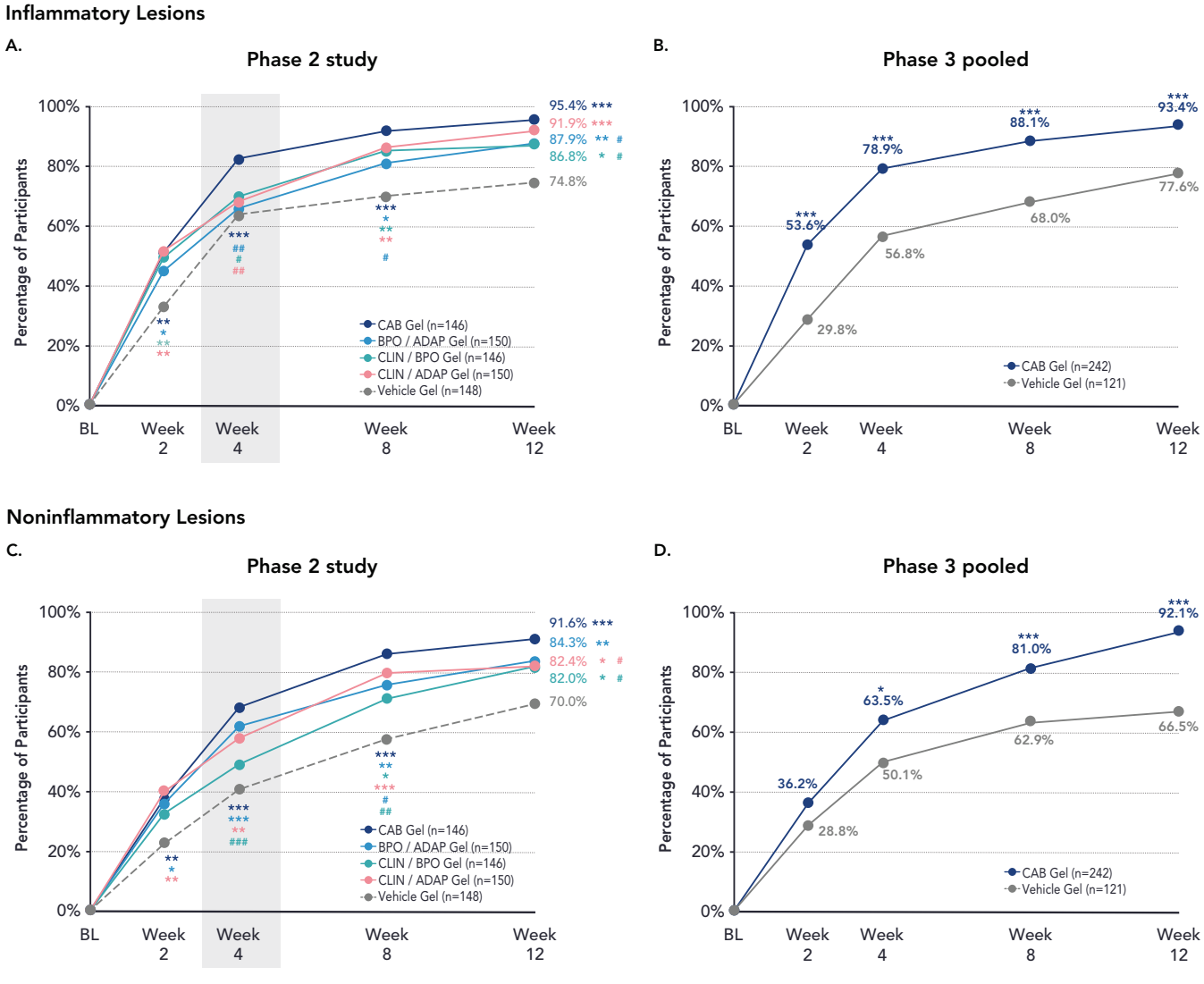
Participant Disposition and Demographics

Detailed baseline demographics and disease characteristics for the individual studies have been previously published.[10,11] A total of 741 and 363 participants were randomized to the phase 2 and the phase 3 studies (pooled), respectively. Participants across all arms/treatment groups of the studies ranged in age from 19.2 to 21.4 years and were predominantly female (phase 2: 61.2%; pooled phase 3: 58.4%), White (69.2%; 73.6%), and had moderate disease (EGSS 3, 84.2%; 91.2%). Treatment compliance was ≥91% in all studies.

Efficacy: ≥33% Reductions

Lesion count reductions of at least one-third occurred rapidly with CAB treatment. By the second post-baseline visit (week 4) in the phase 2 study, 82.7% of participants treated with CAB had at least a 33% reduction in inflammatory lesions, significantly greater than all three dyads and vehicle (dyads, range: 65.9–69.8%; vehicle: 64.1%; $P<0.05$, all; Figure 1A). Similar trends in early reductions in lesion counts were also observed for noninflammatory lesions in the phase 2 study (Figure 1C) and for

FIGURE 1. One-Third Reduction in Lesion Counts (ITT Population, Pooled).



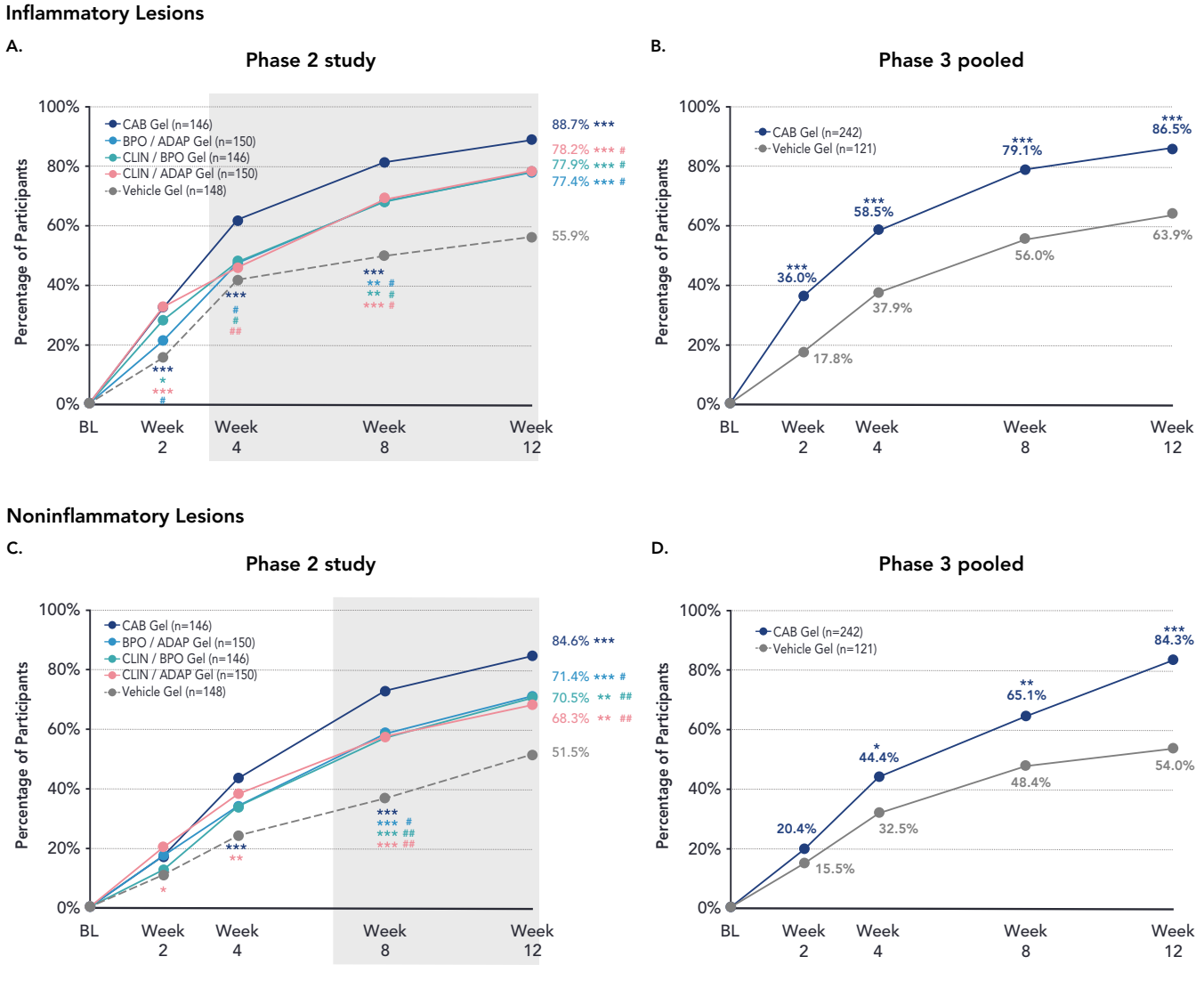
*P<0.05, **P≤0.01, ***P<0.001 active treatment vs vehicle.
#P<0.05, ##P<0.01, ###P≤0.001 dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading at week 4 represents the earliest time point at which CAB produced lesion reductions of ≥33% in a significantly greater percentage of participants compared to at least one of the dyads.

both inflammatory and noninflammatory lesions in the phase 3 studies (Figure 1B, D). By study end at week 12, CAB maintained a higher percentage of patients achieving at least 33% reduction in lesion counts versus the dyads and vehicle, with significant differences versus two of three dyads and vehicle for both inflammatory and noninflammatory lesions (Figure 1 A-D).

Efficacy: ≥50% Reductions

At least one-half reduction in lesion counts with CAB treatment occurred early and was sustained throughout the study. Significantly more participants achieved a one-half reduction in inflammatory lesions with CAB versus dyads as early as week 4, with statistical separation from vehicle occurring as early as

FIGURE 2. One-Half Reduction in Lesion Counts (ITT Population, Pooled).



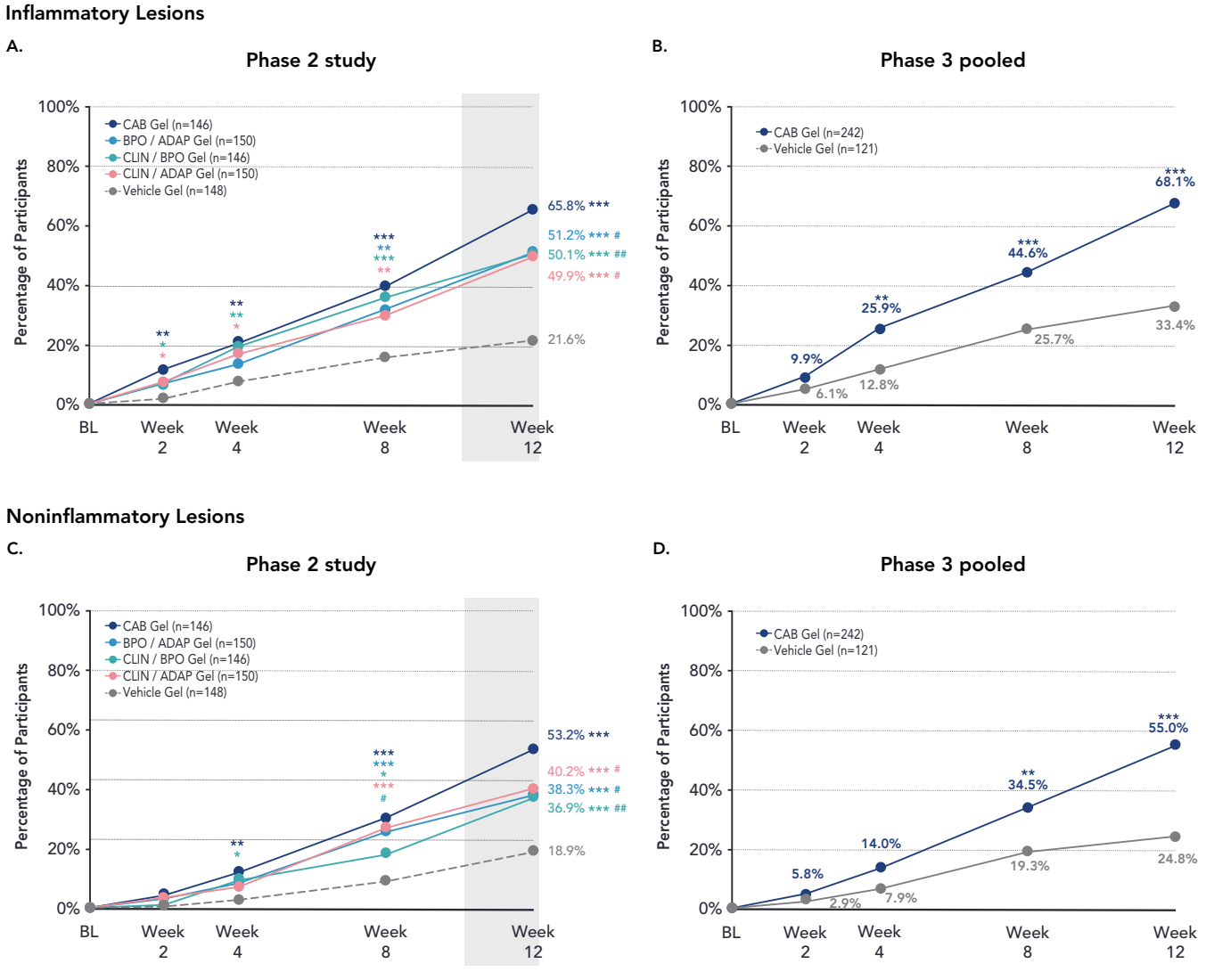
*P<0.05, **P≤0.01, ***P≤0.001 active treatment vs vehicle.
#P<0.05, ##P<0.01, ###P≤0.001 dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading represents the time points at which CAB produced ≥50% lesion reductions in a significantly greater percentage of participants compared to dyads.

week 2 (week 4, CAB: 61.4%; dyads, range: 45.8–47.4%; vehicle: 41.8%; P<0.05, all; Figure 2A). This significant reduction with CAB treatment was maintained at weeks 8 and 12 (81.0% and 88.7%, respectively) versus the dyads and vehicle (range, week 8: 49.6–68.7%; week 12: 55.9–78.2%; P<0.05, all)—a finding replicated in the pooled, phase 3 studies (Figure 2B). Similarly, ≥50% reduction in noninflammatory lesions across the studies occurred in significantly more CAB-treated participants compared to the dyads at weeks 8 and 12 and compared to vehicle at weeks 4 through 12 (Figure 2C, D; P<0.05, all).

Efficacy: ≥75% Reductions

Substantial reductions in lesion counts were achieved by the end of the study at week 12, with nearly two-thirds of participants treated with CAB (65.8%) in the phase 2 study achieving ≥75% reduction in inflammatory lesions, significantly higher than dyads and vehicle (49.9–51.2% and 21.6%; P<0.05, all; Figure 3A). Similar trends in substantial reductions (≥75%) in lesion counts were observed for noninflammatory lesions in the phase 2 study (Figure 3C) and both inflammatory and noninflammatory lesions in the phase 3 studies (Figure 3B, D).

FIGURE 3. Three-Fourths Reduction in Lesion Counts (ITT Population, Pooled).



*** $P \leq 0.001$ active treatment vs vehicle.
# $P < 0.05$, ## $P \leq 0.01$ dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading represents the earliest time point at which CAB produced ≥75% lesion reductions in a significantly greater percentage of participants compared to dyads.

DISCUSSION

Poor treatment adherence typical of acne therapies[3-6] poses a major hurdle to treatment success[3,4] and is exacerbated by the months-long lag in acne improvement discernable by patients following treatment initiation.[4] This post hoc analysis of a phase 2 and two pooled phase 3 trials showed that, as early as week 4, a significantly greater number of participants had at least a 33% reduction in acne lesion counts with the fixed-dose, triple-combination CAB gel compared to constituent dyads and vehicle gel. Lesion count reduction with CAB gel further improved with subsequent study visits, culminating in substantial and significant reductions of at least 75% after 12 weeks of CAB treatment compared to dyads and vehicle gel.This fast-acting feature of CAB—coupled with its optimized efficacy, once a day application, and good tolerability—may positively impact treatment adherence, positioning CAB gel as a desirable treatment option for patients with moderate-to-severe acne.

This post hoc analysis demonstrating rapid and significant acne lesion reductions of varying magnitudes with CAB extends findings from these studies, in which significantly greater reductions in inflammatory and noninflammatory lesions were

observed with CAB treatment versus vehicle gel as early as week 2[10] or week 4.[11] The fast therapeutic action of CAB may be attributed in part to its constituent antibiotic clindamycin phosphate, antimicrobial BPO, and retinoid adapalene, which target three of the four acne pathological mechanisms. Briefly, adapalene modulates cellular keratinization, differentiation, and proliferation, BPO has antimicrobial and mild comedolytic activity along with keratolytic effects, and clindamycin has antibiotic activity.The three drugs in this fixed-dose combination CAB gel may act together to achieve rapid effects on acne lesion counts. Additionally, adapalene and BPO within the polymeric dispersion formulation of CAB are micronized; this allows for even distribution of these active ingredients over the skin and improves penetration into the pilosebaceous unit, thereby potentially boosting treatment efficacy and enabling the rapid therapeutic action of CAB.[15,16]

Comparing these CAB data on acne lesion count reductions of a specific magnitude to those of other commercially available topical dyads containing BPO plus clindamycin or a retinoid is challenging as studies infrequently report such measures. Even so, the percentage of participants achieving thresholds in lesion count reductions was generally higher with CAB compared with commercially available dyads, including clindamycin phosphate 1.2%/BPO 5% gel, adapalene 0.1%/BPO 2.5% gel, clindamycin phosphate 1.2%/tretinoin 0.025% gel, and clindamycin 1%/tretinoin 0.025% hydrogel.[13,17-20] While comparisons cannot be made in the absence of parallel-group studies, a unique design of the phase 2 study of CAB was the inclusion of additional treatment arms with all three dyad combinations within the same vehicle formulation, allowing for a head-to-head comparison. In this study, CAB treatment produced acne lesion count reductions of specific magnitudes (≥33%, 50%, and 75%) in a significantly greater percentage of participants versus all three dyads, demonstrating the benefit of the triple combination over traditional dyad combinations.

Notably, CAB also had a relatively fast onset of action on inflammatory lesions compared to the three dyads in the phase 2 study. Lesion count reductions of both ≥33% and ≥50% occurred in a significantly greater percentage of participants with CAB gel compared to all three dyads as early as week 4 (P<0.05, all), earlier than for noninflammatory lesions (week 8: ≥33% reduction, P<0.05 for two dyads; ≥50% reduction, P<0.05, all). The relatively faster therapeutic effect of CAB on inflammatory lesions could be because BPO, adapalene, and clindamycin all have anti-inflammatory properties. This rapid reduction in inflammatory lesions is crucial: a reduction in inflammatory lesions, which are erythematous and perceivable at a greater viewing distance, is more likely to have a greater impact on patient perception of treatment efficacy[1] and in turn, may promote treatment adherence with CAB gel. Further, the impact of acne on patient quality of life is related to the patient's perception of disease severity, rather than the physician's objective clinical assessment.[21] This rapid reduction in inflammatory lesion counts may thus also have a positive impact on patient quality of life.

A limitation of this post hoc analysis is that it did not include a global measure of acne improvement, such as an assessment of treatment success via EGSS (which have been presented previously for the phase 2 and phase 3 studies[10,11]). However, as treatment success is evaluated as a binary measure (success/failure), it is not possible to evaluate multiple thresholds as was done for this analysis of lesion reductions. Further, it is important to note that the CAB studies were not powered to detect differences in the percentage of patients achieving minimum lesion count reductions between treatment groups. Therefore, P values from the post hoc analyses in this manuscript are for informative purposes only.

CONCLUSION

Therapeutic effect of the fixed-dose, triple-combination clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel on moderate-to-severe acne was rapid and sustained. As early as week 4, acne lesion count reductions of at least 33% and 50% occurred in a significantly greater percentage of participants treated with CAB versus its dyads and vehicle gel. Further, substantial reductions of at least 75% were observed after 12 weeks of CAB treatment. This fast-acting and sustained efficacy of CAB—coupled with its optimized formulation, once a day application, and good tolerability—may positively impact treatment adherence.

DISCLOSURES

Julie Harper has received honoraria from Aclaris, Almirall, BioPharmX, Cassiopea, Cutanea, Dermira, Foamix, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Leon Kircik has served as either a consultant, speaker, advisor, or investigator for Allergan, Almirall, Epi Health, Galderma, Novartis, Ortho Dermatologics, and Sun Pharma. Michael Gold has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Adelaide A. Hebert has received honoraria from Galderma, LEO Pharma, Almirall, Cassiopea, Ortho Dermatologics, Cutanea, Ferrer, Pfizer, and Demira. The UTHealth McGovern Medical School had received research grants from Cassiopea, Demira, and Ortho Dermatologics. Jeffrey L Sugarman is a consultant and speaker for Arcutis, Ortho Dermatologics, Bausch Health, Bristol Myers Squibb, Regeneron, Sanofi, Verrica, Incyte, and Pfizer. Lawrence Green has served as an investigator, consultant, or speaker for Almirall, Cassiopea, Galderma, Ortho Dermatologics, Sol Gel, Sun Pharma, and Vyne. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. Hilary Baldwin has served as an advisor,

investigator, and on speakers' bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. James Q. Del Rosso has served as a consultant, investigator, and/or speaker for Ortho Dermatologics, AbbVie, Amgen, Arcutis, Cutera, Dermavant, EPI Heath, Galderma, Incyte, JEM Health, La Roche-Posay, LEO Pharma, Lilly, L'Oreal, MC2 Therapeutics, Pfizer, Strata, Sun Pharma, and UCB.

ACKNOWLEDGMENT

The study was funded by Ortho Dermatologics. Medical writing support was provided by Kavitha Abiraman PhD and Jacqueline Benjamin PhD of Prescott Medical Communications Group (Chicago, IL) with financial support from Ortho Dermatologics. Ortho Dermatologics is a division of Bausch Health US, LLC.

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NOW AVAILABLE!

ZORYVE®
(roflumilast) topical foam, 0.3%

DOWN TO AGE 9

Effectively control seborrheic dermatitis and simplify treatment with a steroid-free foam.[1]

One foam. Once a day. Anywhere.[1]

SebDone.

DRAMATIC 77% IGA SUCCESS AT WEEK 8[1,2]

Actor portrayal

Trial 203 and STRATUM studies evaluated ZORYVE (n=458) vs vehicle (n=225) once daily for 8 weeks in patients with seborrheic dermatitis. The primary endpoint was IGA Success at Week 8, defined as a score of *Clear* (0) or *Almost Clear* (1) and a ≥2-grade improvement from baseline.

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.[1]

IGA = Investigator Global Assessment

A 2023 Arcutis survey of 93 adults diagnosed with seborrheic dermatitis found that an average of 15 products (including over-the-counter, alternative, and prescription treatments) were reportedly used on a yearly basis.[2]

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

The most common adverse reactions (≥1%) include nasopharyngitis (1.5%), nausea (1.3%), and headache (1.1%).

Please see brief summary of full Prescribing Information for ZORYVE foam on the following page.

See the results at zoryvehcp.com/foam

References: 1. ZORYVE® foam. Prescribing information. Arcutis Biotherapeutics, Inc; 2023.
2. Data on File. Arcutis Biotherapeutics, Inc.

ARCUTIS BIOTHERAPEUTICS

US-COM-154-00125 01/24

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Wash hands after application.

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

ZORYVE foam, 0.3%, is for topical use only and not for ophthalmic, oral, or intravaginal use.

CONTRAINDICATIONS

ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

WARNINGS AND PRECAUTIONS

Flammability

The propellants in ZORYVE foam, 0.3%, are flammable. Avoid fire, flame, and smoking during and immediately following application.

ADVERSE REACTIONS

Clinical Trials Experience

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

In two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 203 and STRATUM), 683 adult and pediatric subjects 9 years of age or older with seborrheic dermatitis were treated with ZORYVE foam, 0.3%, or vehicle foam once daily for 8 weeks. The combined trial population was 79% White, 11% Black, and 5% Asian; for ethnicity, 79% identified as non-Hispanic/Latino and 21% identified as Hispanic/Latino. Fifty percent (50%) were male and 50% were female. The median age was 41 years (range 9 to 87 years). The median body surface area (BSA) affected was 2.5%.

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

Table 1: Adverse Reactions Reported in ≥1% of Subjects with Seborrheic Dermatitis Treated with ZORYVE Foam, 0.3%, for 8 Weeks in Trial 203 and Trial STRATUM

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE foam, 0.3%, in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 30 and 26 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 10 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 16 and 49 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 49 times the MRHD during pregnancy and lactation periods in mice.

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

Clinical Considerations

Labor and delivery

Avoid using ZORYVE foam, 0.3%, during labor and delivery. There are no human studies that have investigated effects of ZORYVE foam, 0.3%, on preterm labor or labor at term; however, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice.

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (30 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (3 times the MRHD on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (10 times the MRHD on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (29 times the MRHD on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (26 times the MRHD on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (16 and 49 times the MRHD on a mg/m^2 basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (16 times the MRHD on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (49 times the MRHD on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (97 times the MRHD on a mg/m^2 basis).

Lactation

Risk Summary

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

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE foam, 0.3%, and any potential adverse effects on the breastfed infant from ZORYVE foam, 0.3%, or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. To avoid direct infant exposure, advise breastfeeding women not to apply ZORYVE foam, 0.3%, directly to the nipple or areola. If applied to the patient's chest, avoid exposure via direct contact with the infant's skin.

Data

Animal data

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

Pediatric Use

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

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

Geriatric Use

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

Hepatic Impairment

Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The systemic exposure of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE foam, 0.3%, is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C). No dosage adjustment is needed in patients with mild (Child-Pugh A) hepatic impairment.

PATIENT COUNSELING INFORMATION

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

Flammability

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

Lactation

Advise patients to use ZORYVE foam, 0.3%, on the smallest area of skin and for the shortest duration possible while breastfeeding. Instruct patients who are breastfeeding not to apply ZORYVE foam, 0.3%, directly to the nipple or areola to avoid direct infant exposure. Instruct patients to avoid inadvertent contact of treated areas with infant skin.

In DERMIS-1 and DERMIS-2, ~40% of patients achieved IGA Success and ~70% of patients achieved I-IGA Success at Week 8.[1]

DERMIS-1 and DERMIS-2 were identical Phase 3 randomized, parallel, double-blind, vehicle-controlled, multicenter studies that evaluated ZORYVE over 8 weeks as a once-daily, topical treatment for plaque psoriasis. Subjects (N=881) were randomized 2:1 to receive ZORYVE cream 0.3% (n=576) or vehicle (n=305) applied once daily for 8 weeks. Eligibility criteria included a diagnosis of mild, moderate, or severe plaque psoriasis and an affected BSA of 2% to 20%. The primary endpoint was IGA Success at Week 8 and a key secondary endpoint was I-IGA Success at Week 8.[1]

IGA Success and I-IGA Success were defined as a score of *Clear* (0) or *Almost Clear* (1) and a ≥2-grade improvement from baseline.[1,2]

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.[1]

BSA = Body Surface Area, IGA = Investigator Global Assessment, I-IGA = Intertriginous-IGA

INDICATION

ZORYVE cream is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 6 years of age and older.

IMPORTANT SAFETY INFORMATION

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

The most common adverse reactions (≥1%) include diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%).

Please see brief summary of full Prescribing Information for ZORYVE cream on the following page.

See the results at zoryvehcp.com/cream

References: 1. ZORVYE® cream. Prescribing information. Arcutis Biotherapeutics, Inc; 2023.
2. Data on File. Arcutis Biotherapeutics, Inc.

ARCUTIS BIOTHERAPEUTICS

US-COM-151-00311 01/24

Brief Summary of Prescribing Information for ZORYVE® (roflumilast) cream, for topical use. See package insert for full Prescribing Information.

INDICATIONS AND USAGE

ZORYVE cream is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 6 years of age and older.

DOSAGE AND ADMINISTRATION

Apply ZORYVE cream to affected areas once daily and rub in completely. Wash hands after application, unless ZORYVE cream is for treatment of the hands.

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

CONTRAINDICATIONS

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

The median age was 47 years (range 6 to 88). The majority of the subjects were male (64%) and White (82%). The median body surface area (BSA) affected was 5.5% (range 2% to 20%). The proportion of subjects who discontinued treatment due to an adverse reaction was 1.0% for subjects treated with ZORYVE cream and 1.3% for subjects treated with vehicle cream. The most common adverse reaction that led to discontinuation of ZORYVE cream was application site urticaria (0.3%).

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

Table 1. Adverse Reactions Reported in ≥1% of Subjects with Plaque Psoriasis Treated with ZORYVE Cream (and More Frequently than Vehicle Cream) for 8 Weeks in Trials DERMIS-1 and DERMIS-2

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

In 594 subjects who continued treatment with ZORYVE cream for up to 64 weeks in open-label extension trials, the adverse reaction profile was consistent with that observed in vehicle-controlled trials.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are insufficient data available on the use of ZORYVE cream in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 9 and 8 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 3 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 5 and 15 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 15 times the MRHD during pregnancy and lactation periods in mice.

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

Clinical Considerations

Labor and delivery

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

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (5 and 15 times the MRHD on a mg/m^2 basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (5 times the MRHD on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (15 times the MRHD on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (29 times the MRHD on a mg/m^2 basis).

Lactation

Risk Summary

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

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

Clinical Considerations

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

Data

Animal data

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

Pediatric Use

The safety and effectiveness of ZORYVE cream for the treatment of plaque psoriasis have been established in pediatric patients 6 years of age and older. Use of ZORYVE cream in pediatric patients 6 to less than 18 years of age is supported by data from two 8-week, vehicle-controlled safety and efficacy trials which included 18 pediatric subjects 6 to 17 years of age, of whom 11 received ZORYVE cream. Use of ZORYVE cream in pediatric patients 12 to 17 years of age is also supported by data from open-label trials of 2 and 24 weeks duration which included 18 pediatric subjects 12 to 17 years of age treated with ZORYVE cream. Use of ZORYVE cream in pediatric patients 6 to less than 12 years of age is also supported by data from one 4-week, open-label, safety and pharmacokinetic (PK) study which included 20 pediatric subjects 6 to less than 12 years of age. The adverse reaction profile in subjects 6 to less than 18 years of age was consistent with that observed in adults.

The safety and effectiveness of ZORYVE cream in pediatric patients below the age of 6 years have not been established.

Geriatric Use

Of the 881 subjects with psoriasis exposed to ZORYVE cream or vehicle for up to 8 weeks in 2 controlled clinical trials, 106 were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted.

Hepatic Impairment

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

PATIENT COUNSELING INFORMATION

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

Lactation

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

doi:10.36849/JDD.7519

March 2024 136 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Survey of Dermatology Practitioners' Opinions and Prescribing Habits of Oral Minoxidil for the Treatment of Androgenetic Alopecia

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ABSTRACT

Background: Utilization of low-dose oral minoxidil has increased in recent years in association with several clinical studies that have shown its efficacy in treating androgenetic alopecia (AGA).
Objective: To assess dermatology providers' attitudes and recommendation behaviors of oral minoxidil for the treatment of AGA.
Methods: An online survey gauging the professional opinions, prescribing behaviors, and use of oral minoxidil was sent using the Orlando Dermatology Aesthetic and Clinical Conference email listserv which included multiple levels of dermatology practitioners including MD/DOs, NPs, and PAs across the United States.
Results: Overall, the survey was sent to 2200 providers, and 201 (9.1%) responses were collected. 81% (n=139) of respondents supported the use of oral minoxidil for AGA. Support varied significantly (*P*=.03) by providers' number of years in practice with those in practice for greater than 30 years with the least amount of support. 92% of respondents (130, n=141) reported feeling comfortable prescribing oral minoxidil, and 83% (116, n=140) found oral minoxidil to be better than its topical formulation. 78% (108, n=139) felt their patients were satisfied with their results, and 89% (124, n=140) felt oral minoxidil was well tolerated by their patients.
Conclusions: This study found that most prescribers use oral minoxidil as a treatment for AGA and find it to be an effective and tolerable option for patients. Support for oral minoxidil was significantly impacted by providers' years in practice.

J Drugs Dermatol. 2024;23(3):136-140. doi:10.36849/JDD.7519

INTRODUCTION

Androgenetic alopecia (AGA) results in progressive hair loss due to miniaturization of hair follicles secondary to androgen influence.[1] AGA affects both men and women and is a common dermatologic complaint that causes significant patient distress. Minoxidil was initially developed as an anti-hypertensive medication and was incidentally found to increase hair density. While its use as an anti-hypertensive has fallen out of favor, it continues to be used in its topical formulation for various alopecic conditions and is one of only two Food and Drug Administration (FDA)-approved medications for AGA. Its mechanism of action for hair growth is not clearly defined; however, it is proposed to work by promoting increased regional scalp blood flow and stimulation of vascular endothelial growth factor.[2] Attention has been drawn to oral minoxidil due to its superior efficacy compared to topical, as well as its cost and ease of use for patients.[3,4] The side effect profile of oral minoxidil is more pronounced than its topical counterpart due to its systemic metabolism; these effects include hypertrichosis, pretibial edema, hypotension, and hypernatremia.[5]

Utilization of low-dose oral minoxidil (LDOM) has increased in recent years in association with several clinical studies that have shown its efficacy in treating AGA and other hair loss conditions.[6,7,8,9] Given that oral minoxidil is not FDA-approved for the treatment of AGA, there is a lack of guidance in prescribing, as well as a lack of consensus regarding its role in treatment. We assessed dermatology providers' attitudes and recommendation behaviors of oral minoxidil for the treatment of AGA.

MATERIALS AND METHODS

An online survey gauging the professional opinions, prescribing behaviors, and use of oral minoxidil was sent using the Orlando Dermatology Aesthetic and Clinical Conference email listserv which included multiple levels of dermatology practitioners including MD/DOs, NPs, and PAs across the United States. Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the George Washington University Institutional Review Board #NCR224464.

RESULTS

Overall, the survey was sent to 2200 providers, and 201 responses were collected (9.1% response rate; Table 1). 81% were Board Certified Dermatologists, and most respondents practiced in a private setting, followed by an academic or VA institution. 82% of respondents reported a primary clinical focus in medical dermatology, followed by 7.5% in cosmetic dermatology.

TABLE 1.

Respondent Demographics					
Gender		**Years In Practice**		**Practice Setting**	
Male	84 (42%)	<10 years	81 (40.7%)	Private Practice	132 (66%)
Female	114 (57%)	11-20 years	38 (19.1%)	Academic institution/ VA	41 (20.5%)
Other/prefer not to answer	2 (1%)	21-30 years	35 (17.6%)	Community Hospital	19 (9.5%)
Total	200	>30 years	45 (22.6%)	HMO	2 (1%)
--	--	--	--	Other	6 (3%)
--	--	Total	199	Total	200
Gender		**Title**		**Clinical Focus**	
East North Central[a]	25 (12.5%)	Board Certified Dermatologist (MD/DO)	162 (81.4%)	Medical Dermatology	164 (82.4%)
East South Central[b]	8 (4.0%)	Dermatology Resident	10 (5.0%)	Cosmetic Dermatology	15 (7.5%)
Mid-Atlantic[c]	31 (15.5%)	Physician Assistant/Associate (PA)	15 (7.5%)	Dermatologic Surgery	8 (4.0%)
Mountain[d]	14 (7.0%)	Nurse Practitioner (NP)	5 (2.5%)	Dermato-pathology	0 (0%)
New England[e]	15 (7.5%)	Other	7 (4.0%)	Other	12 (6.0%)
Pacific[f]	29 (14.5%)	Total	199	Total	199
South Atlantic[g]	49 (24.5%)	--	--	--	--
West North Central[h]	8 (4.0%)	--	--	--	--
West South Central[i]	15 (7.5%)	--	--	--	--
Total	200	--	--	--	--

[a]IN, IL, MI, OH, WI; [b]AL, KY, MS, TN; [c]NJ, NY, PA; [d]AZ, CO, ID, NM, MT, UT, NV, WY; [e]CT, ME, MA, NH, RI, VT; [f]AK, CA, HI, OR, WA; [g]DE, DC, FL, GA, MD, NC, SC, VA, WV; [h]IO, KS, MN, MO, NE, ND, SD; [i]AR, LA, OK, TX

81% of respondents supported the use of LDOM for AGA. Support varied significantly (*P*=.03) by providers' number of years in practice with those in practice for greater than 30 years with the least amount of support (Table 2). Significant differences in support of oral minoxidil use did not apply when stratifying by region. 75% of respondents currently prescribe LDOM to their patients. 1.25 mg once daily was the most frequently reported starting dose (56 [39%], n= 142) followed by 2.5 mg once daily (25 [18%], n=142) and then 0.25 mg once daily (18 [13%], n=142). Twenty-six respondents reported using LDOM as a first-line therapy (Table 3). The difference in first-line use stratified by years in practice was statistically significant (*P*=.03) with 27.3% of respondents in practice fewer than 10 years using LDOM as a first-line therapy. Significant differences in oral minoxidil usage did not persist when stratified by region.

81% of respondents (112, n=139) reported using topical minoxidil before the oral formulation, as well as oral finasteride (59 [42%], n=139), spironolactone (61[44%], n=139), and platelet-rich plasma injections (25 [18%], n=139). 44% of respondents (62, n=141) who prescribe LDOM recommended using 5% topical minoxidil at least once daily in addition to the oral medication, while 29% (41, n=141) recommended that patients avoid topical minoxidil while taking oral minoxidil.

31% (44, n=142) of providers who prescribe oral minoxidil found it to be very effective for AGA, while 44% found it to be somewhat effective (63, n=142), and 23% were uncertain of its efficacy (32, n=142). Regarding medication discontinuation, 38% of respondents reported no accounts of discontinuation in patients, whereas 24% cited hypertrichosis and 17% cited a lack of clinical improvement as the primary reason for discontinuation (Figure 1). 77% (109, n=142) of respondents indicated seeing an initial increase in hair density within 6 months of drug initiation, compared to 10% (14, n=142) who saw improvement after 6 months.

92% of respondents (130, n=141) reported feeling comfortable prescribing oral minoxidil, and 83% (116, n=140) found LDOM to be better than its topical formulation. 78% (108, n=139) felt their patients were satisfied with their results, and 89% (124, n=140) felt oral minoxidil was well tolerated by their patients.

44 respondents (22%, n=201) did not prescribe oral minoxidil, citing unfamiliarity with its use (34%), concerns about safety (68%), lack of FDA-approval (39%), and side effects (55%) (Figure 2). Interestingly, 61% of these respondents (27, n=44) felt that oral minoxidil caused at least some improvement in hair density, while no respondent felt oral minoxidil caused a worsening in hair density (0, n=44).

TABLE 2.

Do You Support the Use of Oral Minoxidil for AGA?				
	Yes	No	Uncertain	
Total	162 (81.0%)	16 (8.0%)	20 (11.0%)	200
Years in Practice				
<10 years	70 (86.4%)	2 (2.5%)	9 (11.1%)	
11-20 years	31 (81.6%)	1 (2.6%)	6 (15.8%)	*P*=.03
21-30 years	28 (80.0%)	5 (14.3%)	2 (5.7%)	
>30 years	32 (71.1%)	8 (17.8%)	5 (11.1%)	
Region				
East North Central[a]	21 (84.0%)	2 (8.0%)	2 (8.0%)	
East South Central[b]	4 (66.7%)	1 (16.7%)	1 (16.7%)	
Mid-Atlantic[c]	24 (77.4%)	4 (12.9%)	3 (9.7%)	
Mountain[d]	12 (85.7%)	1 (7.6%)	1 (7.6%)	
New England[e]	14 (93.3%)	0 (0.0%)	1 (6.7%)	*P*=.98
Pacific[f]	23 (79.3%)	3 (10.3%)	3 (10.3%)	
South Atlantic[g]	39 (79.6%)	3 (6.1%)	7 (14.3%)	
West North Central[h]	7 (87.5%)	0 (0.0%)	1 (12.5%)	
West South Central[i]	13 (86.7%)	1 (6.7%)	1 (6.7%)	

[a]IN, IL, MI, OH, WI; [b]AL, KY, MS, TN; [c]NJ, NY, PA; [d]AZ, CO, ID, NM, MT, UT, NV, WY; [e]CT, ME, MA, NH, RI, VT; [f]AK, CA, HI, OR, WA; [g]DE, DC, FL, GA, MD, NC, SC, VA, WV; [h]IO, KS, MN, MO, NE, ND, SD; [i]AR, LA, OK, TX

TABLE 3.

Oral Minoxidil as 1st-Line Therapy			
	1st Line Therapy	Total[a]	
Total	26 (18.7%)	139	
Years in Practice			
<10 years[a]	18 (27.3%)	66	
11-20 years[b]	2 (6.9%)	29	*P*=.03
21-30 years[c]	4 (16.0%)	25	
>30 years[d]	2 (6.9%)	29	
Region			
East North Central[b]	5 (27.8%)	18	
East South Central[c]	0 (0.0%)	4	
Mid-Atlantic[d]	2 (8.3%)	24	
Mountain[e]	3 (27.3%)	11	
New England[f]	4 (30.8%)	13	*P*=.58
Pacific[g]	5 (22.7%)	22	
South Atlantic[h]	7 (18.4%)	38	
West North Central[i]	0 (0.0%)	3	
West South Central[j]	0 (0.0%)	12	

[a]respondents who prescribe oral minoxidil for AGA; [b]IN, IL, MI, OH, WI; [c]AL, KY, MS, TN; [d]NJ, NY, PA; [e]AZ, CO, ID, NM, MT, UT, NV, WY; [f]CT, ME, MA, NH, RI, VT; [g]AK, CA, HI, OR, WA; [h]DE, DC, FL, GA, MD, NC, SC, VA, WV; [i]IO, KS, MN, MO, NE, ND, SD; [j]AR, LA, OK, TX

FIGURE 1. Prescribers of oral minoxidil were asked to indicate the most common reason for patient discontinuation (n=139).

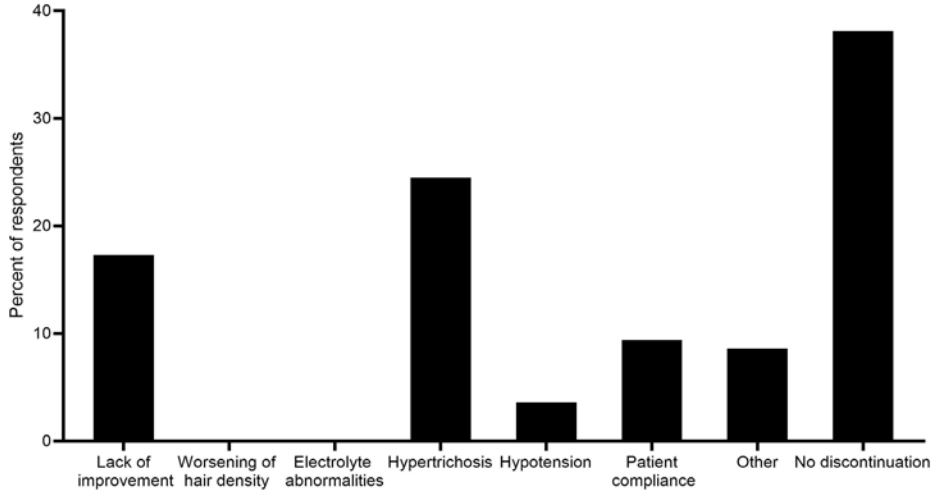
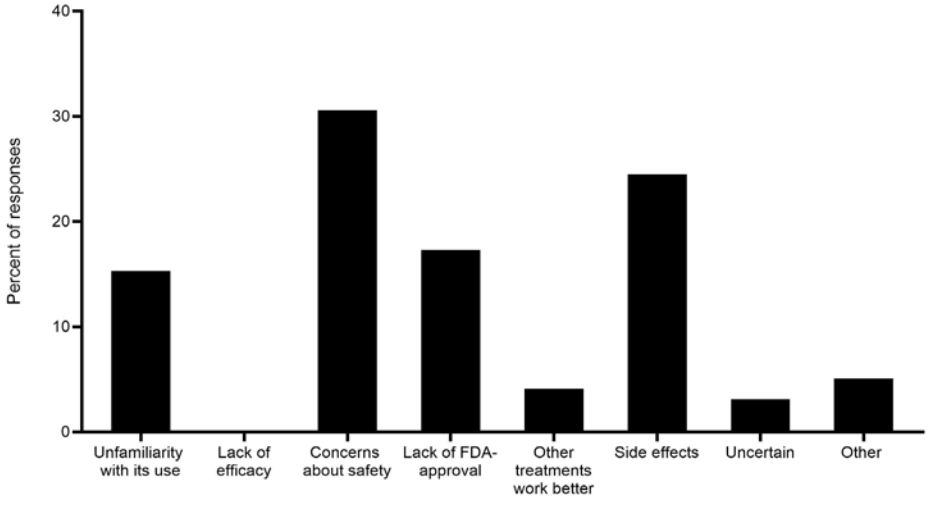


FIGURE 2. Respondents who indicated they did not prescribe oral minoxidil were asked to select one or more reasons why they did not prescribe oral minoxidil (n=98).



DISCUSSION

Our results suggest that LDOM is viewed favorably by most dermatology providers, even among those who do not prescribe it. Most respondents indicated they already use oral minoxidil as part of their treatment of AGA, both on its own and in conjunction with other therapies. When analyzing support for oral minoxidil, as well as its use as a first-line therapy, significant differences existed between providers' years in practice. We found that those practicing the longest were more reticent to support or use oral minoxidil as a first-line treatment. Concerns about safety and side-effects were the most cited reasons among those who did not prescribe oral minoxidil and likely played a role in the reticence among those who do prescribe oral minoxidil. These differences did not persist in analysis by US region, which further emphasizes the role of years in practice in attitudes towards oral minoxidil.

Our results are consistent with previous studies demonstrating oral minoxidil to be more effective than topical minoxidil, though most of our respondents continue to use topical minoxidil before prescribing its oral formulation.[4] We theorize this is due topical minoxidil's over-the-counter availability, FDA-approval, and side-effect profile. Our results do also suggest a positive opinion of concomitant oral and topical minoxidil usage, though more research is needed to understand the clinical benefit of simultaneous use.

While most providers prescribed a starting dose of either 1.25 mg or 2.5mg once daily, there was a broad range of responses from 0.25 mg once daily to 5 mg twice daily. This variability highlights a lack of guidance and consensus among dermatologists when initiating oral minoxidil therapy.

Limitations of this study include self-selection bias and lack of randomization, given that respondents were contacted through a mailing list from a particular dermatology conference. Furthermore, the small sample size reduces the generalizability and power of the study, and the low response rate can introduce sampling bias. Advertising the survey through additional means, including other professional mailing lists or social media posts, would reach more respondents and address the small sample size in future studies. When assessing the starting dose for oral minoxidil, the answer choices were not separated by sex, which may have skewed the results to either a higher or lower dose, depending on whether providers prescribe differing doses based on patient sex.

CONCLUSION

Many prescribers use oral minoxidil as a treatment for AGA and find it to be an effective and tolerable option for patients. Providers' years in practice affected their support for oral minoxidil. More research is needed to further characterize oral minoxidil's use and role in the treatment of AGA.

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.8172

March 2024 141 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Natural Moisturizing Factor-Enriched Formulations Compared to a Ceramide-Based Cream

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ABSTRACT

Background: We aimed to investigate the effects of 2 ceramide plus natural moisturizing factor-enriched formulations compared to a ceramide-based cream on skin moisturization.

Methods: Two double-blinded comparative studies were conducted, which enrolled 35 (n=29 females, n=6 males) and 33 (n=21 females, n=12 males) participants, respectively. Participants applied ceramide plus natural moisturizer cream or ceramide-based cream (study 1) or applied ceramide plus natural moisturizing factor lotion or ceramide-based cream (study 2) to each of their lower legs for 10 days with a 5-day regression period (no moisturizer applied). Skin hydration by corneometry after bilateral application was conducted once daily for each leg in both groups.

Results: An increase in corneometer units vs baseline for the ceramide plus natural moisturizing factor-enriched cream and natural moisturizing factor-enriched lotion were greater than the increase vs baseline for the ceramide-based cream at days 10 and 15; with an overall statistical significance in favor of the ceramide plus natural moisturizing factor-enriched formulations at day 10.

Conclusions: The marked improvement in skin moisturization following utilization of the ceramide plus natural moisturizing factor-enriched cream and lotion compared to the ceramide-based cream can be attributed to the inherent properties of the natural moisturizing factors. These properties are known to maintain the humectancy and intercellular lipid membrane of the stratum corneum, which directly improves the permeability barrier function of human skin in reducing transepidermal water loss.

J Drugs Dermatol. 2024;23(3):141-145. doi:10.36849/JDD.8172

INTRODUCTION

The skin is a complex barrier composed of tightly packed junctions consisting of 3 parts: stratified epidermis, dermis, and subcutaneous tissue.[1] A primary function of the skin is to maintain a physical barrier against external exposures, preventing entry of harmful substances and maintaining physiologic water content.[1] The permeability barrier function of the epidermis prevents excessive fluid gain or loss from the body occurring within the stratum corneum (SC), the outer portion of the epidermis, which is collectively active in maintaining multiple skin barrier functions necessary to sustain healthy skin.[2] When the skin is compromised by exogenous and/or external environmental exposures, permeability barrier function is impaired. This leads to increased transepidermal water loss (TEWL), which predisposes the skin to adverse sequelae of xerosis; microfissuring; decreased resiliency; natural elastic recoil, scaling, and hyperkeratosis; and an increased risk of microbial infections.[2-4] The water content inside the SC is essential to maintaining the structural and functional integrity of the skin and the multiple functions of the skin barrier.[3,5]

The SC usually is described as a brick-and-mortar complex filled with keratin cells and a lipid matrix, which sounds fixed in its structure, but is dynamic, responds to exposures, and corrects itself with innate repair mechanisms.[2,6,7] Specific enzymes in the epidermis act on phospholipids to synthesize ceramides, free fatty acids, and cholesterol in a physiologic ratio of relative concentrations, thus regulating the permeability and structural functions of the SC.[8,9] Ceramides are the predominant lipid of the SC, making up approximately 50% of the intracellular content by mass.[10] However, the SC contains additional key elements associated with barrier functionality, including urea, lactic acid, and filaggrin-derived amino acids and amino acid metabolites (ie, pyrrolidone carboxylic acid [PCA] and urocanic acid [UCA]).[11] These components, known collectively as the natural moisturizing factor (NMF), are important in regulating SC homeostasis. They act as "nature's humectant" to retain physiologic epidermal water content and maintain the structural integrity of keratin bundles in corneocytes essential for reducing TEWL.[12] Importantly, other hydrolytic enzymes in the SC are responsible for desmolytic activity, which allows for

the invisible process of normal skin desquamation via individual separation of corneocytes. When there is diminished SC water content below a physiologic level, these hydrolytic enzymes function sub-optimally, leading to incomplete separation and clumping of individual corneocytes, which can be perceived visibly as scaling.[2]

Topical skincare products, including creams, lotions, and ointments have been widely used to protect and maintain skin barrier structure and function. A major emphasis of optimized moisturizer formulations has been to incorporate ingredients that reduce TEWL (occlusives, NMFs) and to replenish and/or support functional components (NMFs, ceramides antioxidants, others).[4,13] Due to their established major importance in skin barrier functions, and their impairment and/or quantitative decrease in several environmental or disease-associated scenarios, ceramides are frequently included ingredients in many topical skin moisturizers; many formulations also contain NMFs to further enhance the maintenance of skin barrier function by including compounds found in the innate epidermal barrier.[4,13,14]

In the present study, we describe the head-to-head clinical comparison of 2 ceramide plus NMF-enriched formulations (cream and lotion) and a ceramide-based formulation (cream) on skin hydration in 2 double-blinded comparative studies after 10 days of daily bilateral application followed by 5 days of no moisturizer use for regression analysis.

MATERIALS AND METHODS

Test Products

Study 1: Moisturizer A, Ceramide plus natural moisturizing factor-enriched cream (Eucerin Advanced Repair Cream, Beiersdorf Inc.); Moisturizer B, Ceramide-based cream (CeraVe Moisturizing Cream, L'Oreal Group).

Study 2: Moisturizer C, Ceramide plus natural moisturizing factor-enriched lotion (Eucerin Advanced Repair Lotion, Beiersdorf Inc.); Moisturizer B, Ceramide-based cream (CeraVe Moisturizing Cream, L'Oreal Group).

Institutional Review Board

Prior to participant enrollment for the study, the protocol and informed consent form (ICF) for this study were reviewed and approved by IntegReview Institutional Review Board (IRB) on September 26, 2016. IntegReview IRB, located in Austin, Texas, is a duly constituted IRB under Title 21 Code of Federal Regulations (CFR) Parts 50 and 56.

Informed Consent

Written informed consent conforming to 21 Code of Federal Regulations (CFR) 50.25 was obtained from each adult participant (at least 18 years old) or the parent/guardian of each minor participant (under the age of 18 years) prior to enrollment in the study. The original signed ICF for each patient participating in the study was retained in the study file and each patient received a copy of the signed form.

Study Design

Both studies were bilateral and double-blinded and were conducted from October 5, 2016, to November 2, 2016, at the Thomas J. Stephens & Associates, Inc. Colorado Research Center, Colorado Springs, Colorado.

Participants

Study 1: The first study included 35 participants (Male, n=6; Female, n=29) ages 16-70 years old (Mean, 57.1); 25% of the group (n=9) had mild dryness on the legs, and approximately 75% (n=26) had moderate-to-severe dryness on the legs.

Study 2: The second study included 33 participants (Male, n=12; Female, n=21) ages 16-70 years old (Mean, 50.9). Approximately 50% of the group (n=16) had mild dryness, and approximately 50% (n=17) had moderate-to-severe dryness on the legs.

Test Area and Application Procedures

Study 1: During the 10-day usage period of the study, participants applied Moisturizer A on the randomly assigned (right or left) leg and Moisturizer B on the opposite leg, once daily as directed. After 10 days, participants discontinued the use of the moisturizer and participated in a 5-day regression period during which time no moisturizer was applied.

Study 2: During the 10-day usage period of the study, participants applied Moisturizer B on the assigned (right or left) leg and Moisturizer C on the opposite leg, once daily as directed. After 10 days, participants discontinued the use of the moisturizer and participated in a 5-day regression period during which time no moisturizer was applied.

Enrollment Procedures

Prior to the start of the study, potential participants were screened over the telephone for eligibility criteria. Female and male participants between ages 16 and 70 years old were scheduled for eligibility screening at the clinic. Prospective participants were advised not to shave their legs and to avoid the application of any topical moisturizing product and use of cleansers with moisturizing properties on the legs for at least 3 days prior to visit 1.

At visit 1 (baseline), each prospective participant or the parent/guardian of minor prospective participants read and signed the informed consent form after the nature of the study was explained and any study-related questions were answered. Minor prospective participants (under the age of 18 years) signed an assent form indicating their agreement to participate

in the study. In addition, prospective participants or parents/guardians completed an eligibility and health questionnaire. Prospective participants who signed the initial paperwork were assigned a screening number.

Prospective participants acclimated to ambient temperature and humidity conditions for at least 15 minutes prior to participating in clinical procedures. During the study, applicable waiting/instrumentation rooms were maintained at a temperature of 68°F to 75°F and relative humidity from 35% to 65%.

Application of Moisturizers

Participants were distributed pre-weighed units of the test material and instructed to apply it to each leg according to the following instructions:

- Apply a sufficient amount of moisturizer (about the size of a half-dollar coin) to the appropriate leg (starting at the kneecap and down to the ankle) once daily in the evening for 10 days. Please make sure the moisturizer covers the entire lower leg area. Wash and dry hands between applications of each test material (one moisturizer per leg) to avoid cross-contamination of the sites.

Regression Period

After completion of the day 10 procedure, participants were instructed not to shave their legs, apply any moisturizing products, or use cleansers with moisturizing effects on the legs for a 5-day regression period during which no moisturizer was used.

Corneometer Measurements

At baseline, day 10, and day 15, triplicate corneometer (CM 825, Courage & Khazaka, Germany) measurements were taken on both legs of each participant at the midline between the knee and ankle of the lateral side.

Statistical Analysis

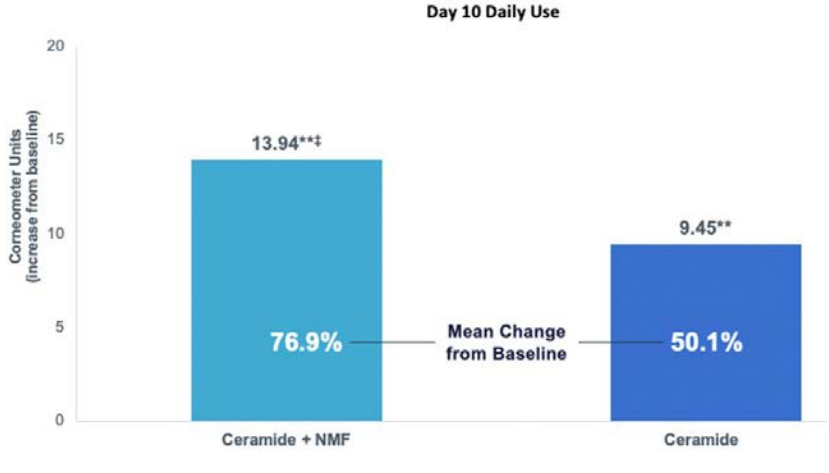
Triplicate corneometer measurements for each participant, location, and time point were averaged prior to statistical analysis. All results are presented as the percent mean change from baseline. Significance of mean change from baseline and comparison between groups was tested using a paired t-test. All statistical tests were 2-sided at a significant level of alpha=0.05. *P*-values were reported to 3 decimal places. No multiple testing corrections were considered in the study. Statistical analyses were performed using SAS software version 9.40 series (SAS Statistical Institute).

RESULTS

Ceramide Plus NMF Cream vs Ceramide Cream

Assessment of skin hydration by corneometer was performed on day 10 after once daily use of ceramide plus NMF or ceramide cream, and a 5-day regression period of no daily moisturization (day 15). Daily moisturization for 10 days with the ceramide plus NMF cream resulted in a 76.9% increase in corneometer units compared to baseline ($P<0.001$), while daily moisturization of the ceramide cream resulted in an increase of 50.1% compared to baseline ($P<0.001$), with an overall statistical significance in favor of the ceramide plus NMF cream vs the ceramide cream ($P<0.001$) (Figure 1).

FIGURE 1. Clinical evaluation of skin hydration after 10 days of daily moisturization. Thirty-five participants (Male, n=6; Female, n=29) ages 16 to 70 years old (Mean, 57.1), 25% (n=9) with mild dryness on the legs and approximately 75% (n=26) with moderate-to-severe dryness on legs, applied ceramide plus NMF cream on the assigned (right or left) leg and ceramide cream on the opposite leg, once daily for 10 days, as directed. At baseline and day 10, triplicate corneometer (CM 825, Courage & Khazaka) measurements on both legs of each participant were taken at the midline between the knee and ankle of the lateral side and increase from baseline corneometer units were plotted, with mean change from baseline calculated.



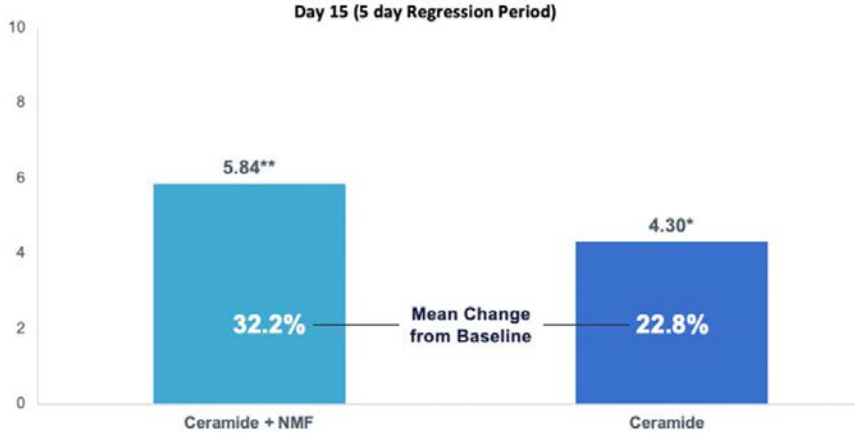
**Statistically significant improvement compared to baseline ($P<0.001$). ‡Statistically significant difference between treatments in favor of Ceramide plus NMF ($P<0.001$).

The lasting effect of Improvement in skin hydration was evaluated at day 15 (5-day regression with no additional moisturization). The ceramide plus NMF cream 10-day moisturization plus 5-day regression yielded a 32.2% increase from baseline corneometer units (P<0.001), while the ceramide cream yielded a 22.8% increase from baseline corneometer units (P<0.05) (Figure 2).

Ceramide Plus NMF Lotion vs Ceramide Cream

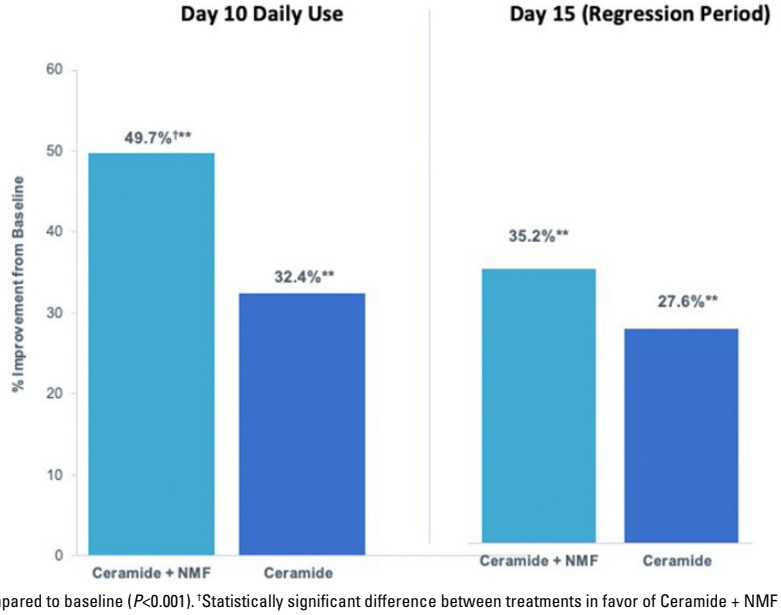
To address the misconception that creams are always more efficacious than lotions, we evaluated the clinical efficacy of improvement in skin hydration after 10 days of daily use of the ceramide plus NMF lotion compared to the ceramide cream, followed by corneometer assessment at day 15 following a 5-day

FIGURE 2. Clinical evaluation of skin hydration on day 15 (5-day regression period with no moisturization). Thirty-five participants (Male, n=6; Female, n=29) ages 16 to 70 years old (Mean, 57.1), 25% with (n=9) mild dryness on the legs and approximately 75% (n=26) with moderate-to-severe dryness on the legs, applied ceramide plus NMF cream on the assigned (right or left) leg and ceramide cream on the opposite leg, once daily for 10 days, as directed, followed by a 5-day regression period of no moisturization. At baseline and day 15, triplicate corneometer (CM 825, Courage & Khazaka) measurements were taken on both legs of each participant at the midline between knee and ankle of the lateral side, and increase from baseline corneometer units were plotted, with mean change from baseline calculated.



**Statistically significant improvement compared to baseline (P<0.001). *Statistically significant improvement compared to baseline (P<0.05).

FIGURE 3. Clinical evaluation of skin hydration after 10 days of daily moisturization and on day 15 (5-day regression period with no moisturization). Thirty-three participants (Male, n=12; Female, n=21) ages 16 to 70 years old (Mean, 50.9), some with mild dryness on the legs (n=16) and some with moderate-to-severe dryness on legs (n=17), applied ceramide plus NMF lotion on the assigned (right or left) leg and ceramide cream on the opposite leg, once-daily as directed for 10 days followed by a 5-day regression period of no moisturization. At baseline, day 10, and day 15, triplicate corneometer (CM 825, Courage & Khazaka) measurements were taken on both legs of each participant at the midline between the knee and ankle of the lateral side, and increase from baseline corneometer units were plotted, with mean change from baseline calculated.



**Statistically significant improvement compared to baseline (P<0.001). †Statistically significant difference between treatments in favor of Ceramide + NMF lotion (P<0.05).

regression period, similar to the methodologies used in the ceramide plus NMF cream vs ceramide cream study described above. Daily moisturization for 10 days with the ceramide plus NMF lotion resulted in a 49.7% increase in corneometer units compared to baseline (P<0.001), while daily moisturization of the ceramide cream resulted in an increase of 32.4% compared to baseline (P<0.001), with an overall statistical significance in favor of the ceramide plus NMF lotion vs the ceramide cream (P<0.05) (Figure 3). Once again, the lasting effect of improvement in skin hydration was evaluated at day 15 (5-day regression with no additional moisturization). The ceramide plus NMF lotion 10-day moisturization plus 5-day regression yielded a 35.2% increase from baseline corneometer units (P<0.001), while the ceramide cream yielded a 27.6% increase from baseline corneometer units (P<0.05) (Figure 3).

DISCUSSION

While the focus on barrier repair with topical moisturization has often centered on the inclusion of ceramides in formulations, the utilization of additional ingredients, including NMFs, has not received adequate attention to their potential importance in moisturizer formulations. In this study, we demonstrate the statistical superiority of both a ceramide plus NMF cream and a ceramide plus NMF lotion compared to a ceramide cream based on recognized objective methods of testing hydration after 10 days of daily application. While all 3 formulations improved skin hydration, as indicated by the significant increase in corneometer units from baseline, the ceramide plus NMF cream and ceramide plus NMF lotion demonstrated a significantly higher increase in skin hydration as compared to baseline and as compared to the ceramide cream.

Ceramides and NMFs are major SC components that contribute to maintaining skin hydration.[15] NMFs originate from the breakdown of filaggrin and include hydrophilic amino acids, and their derivatives such as PCA, UCA, lactic acid, sugars, organic acids, peptides, and urea, which collectively are associated with the establishment of a physiologic water gradient in the SC.[16-18]

The increased role of NMFs in skin barrier function continues to be elucidated, with recent studies demonstrating the importance of NMFs in skin barrier function in atopic dermatitis (AD).[19] Decreases in NMF are attributed to both intrinsic and extrinsic factors, which are associated with xerotic skin, increased surface pH, and increased risk for worsening of AD.[19] The addition of NMFs in well-formulated topical moisturizers has previously been shown to augment skin hydration by supporting the maintenance of water content in dehydrated conditions, thus retaining the optimal fluidity and function in SC lipid and protein components.[20] Exposure of the skin to commonly encountered external daily conditions that can impair epidermal barrier function, including washing, showering, and bathing, or the use of occlusive sanitary products such as diapers, which can deplete important hydrophilic compounds of the SC, including NMFs. This depletion markedly affects the ability of the SC to attract and maintain water, leading to a cascade of events that can steadily progress to severe xerosis and eczematous dermatitis, both associated with pruritus and increased potential for microbial colonization.[21,22] These data and the results of our study suggest that the utilization of a moisturizer (cream or lotion) that contains both ceramides and NMFs may be a more optimal formulation, compared to a ceramide cream alone, for maintaining skin hydration, improving barrier function, and decreasing the clinical sequela associated with dry skin.

DISCLOSURES

Dr Baldwin has acted as an investigator, consultant, and/or speaker for Almirall, Bausch, Cassiopea, EPI Health, Galderma, La Roche-Posay, L'Oreal, Mayne Pharma, Sol-Gel, Sun Pharma, and Vyne. Dr Del Rosso has served as a consultant, investigator, and/or speaker for Abbvie, Almirall, Amgen, Arcutis, Bausch Health (Ortho Dermatologics), Beiersdorf, Dermavant, EPI Heath, Ferndale, Galderma, Incyte, JEM Health, LaRoche Posay, LEO Pharma, Lilly, Loreal, MC2 Therapeutics, Novan, Pfizer, Regeneron, Sanofi, Se0nte, SolGel, Sun Pharma, UCB and Unilever. Dr Arrowitz is an employee of Beiersdorf Inc.

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doi:10.36849/JDD.7743

March 2024 146 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Safety and Efficacy of Minoxidil Treatment in Scarring Alopecia: A Scoping Review

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ABSTRACT

Background: Topical minoxidil (TM) has been a cornerstone in treating various hair loss disorders, while low-dose oral minoxidil (LDOM) is emerging as an effective alternative. Despite their widespread use, there is a notable gap in the literature regarding their use in treating scarring alopecia.

Objective: This study evaluates the efficacy and safety of TM and LDOM in managing scarring alopecia.

Methods: A systematic literature search identified relevant studies on TM and LDOM use in central centrifugal cicatricial alopecia, frontal fibrosing alopecia, lichen planopilaris, and traction alopecia. Key metrics included disease stabilization, hair thickness improvement, hair regrowth, and side effect profiles.

Results: Analysis of the selected studies revealed mixed outcomes. Most participants experienced benefits in terms of disease stabilization and hair regrowth with TM and LDOM. The majority of cases reported good tolerability of the treatment, although some side effects were noted.

Conclusion: TM and LDOM show promise in scarring alopecia treatment, demonstrating benefits in disease stabilization and hair regrowth. Despite these positive indications, the variability in results and reported side effects underline the need for further research to establish their consistent efficacy and safety profiles in scarring alopecia treatment.

J Drugs Dermatol. 2024;23(3):146-151. doi:10.36849/JDD.7743

INTRODUCTION

Topical minoxidil (TM) has been widely used to treat various hair loss conditions since it was first approved in the United States in 1986.[1] More recently, low dose oral minoxidil (LDOM) has been increasingly utilized to treat scalp hair loss. This is partly due to its convenience and possible higher bioavailability in its active form (minoxidil sulfate) as it is more efficiently metabolized in the liver rather than the hair follicle with TM.[2,3]

While both LDOM and TM are being prescribed for both scarring and non-scarring alopecia, only TM is currently approved by the Food and Drug Administration (FDA) in the United States. Furthermore, the approved indication is androgenetic alopecia, which is a non-scarring alopecia. LDOM has not been studied or reviewed by the FDA as a treatment for hair disorders. Additionally, most studies of LDOM or TM have focused on non-scarring alopecias such as alopecia areata and androgenetic alopecia.[3]

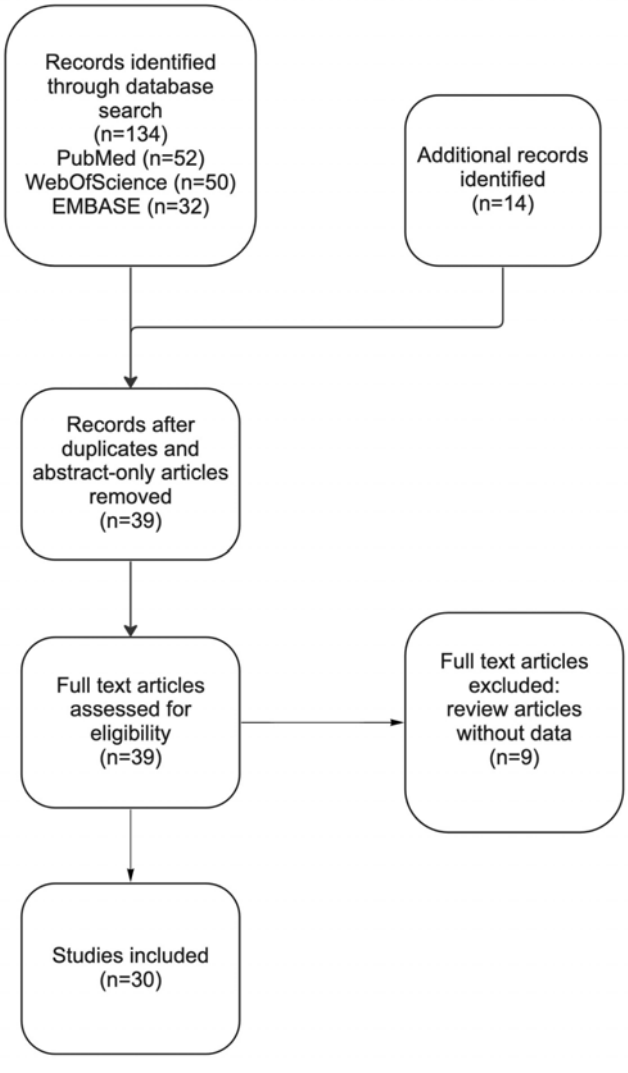
Scarring alopecia is responsible for approximately 10 to 30% of hair loss cases.[4,5] Unlike non-scarring alopecias, hair follicles can be irreversibly damaged in scarring conditions by the destruction of stem cells in the hair bulge region, which warrants prompt and proactive treatment to reduce disease activity and restore hair thickness and density as much as possible.[5,6]

TM and LDOM are frequently prescribed to patients with scarring alopecia based on extrapolated data from patients with non-scarring hair loss and anecdotal clinical experience. Multiple small retrospective studies report the safety and efficacy of TM and LDOM in the management of scarring alopecias but no comprehensive review of such data has been published. Here, we review oral and topical minoxidil for the management of scarring alopecia.

MATERIALS AND METHODS

A comprehensive literature search across the PubMed, Embase, and Web of Science databases was performed to identify

FIGURE 1. Flow diagram for article selection.



English-language articles published up to September 2022 using the terms "scarring alopecia", "frontal fibrosing alopecia", "lichen planopilaris", "central centrifugal cicatricial alopecia", "pseudopelade of Brocq", "folliculitis decalvans", "dissecting folliculitis", or "traction alopecia" for disease conditions, and "oral minoxidil" or "topical minoxidil" for treatment.

Medical Subject Headings (MeSH) terms were used for the comprehensive search of synonyms of each keyword. Inclusion criteria were as follows: English text available, scarring alopecia study population, and treatment with topical or oral minoxidil. A board-certified dermatologist (R.F.) reviewed all resulting articles and excluded duplicates and non-relevant articles. The reference lists were then manually reviewed and additional articles meeting the criteria were identified upon review of article references and included (Figure 1).

RESULTS

Oral Minoxidil

A total of nine studies with 91 patients were found discussing the use of LDOM as a treatment for scarring hair loss, including central centrifugal cicatricial alopecia (CCCA), frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), and traction alopecia (TA) (Table 1). Of note, only a handful of literature was available regarding LDOM treatment given its relatively recent introduction to hair loss treatment.

All patients were female, approximately 30 to 60 years old. Minoxidil dosing varied between 0.25 to 5 mg/day, all below hypertension treatment doses. Seven articles reported positive results such as disease stabilization, improved hair thickness, or regrowth of hair.[7-13] One study reported a response to minoxidil monotherapy, however; this article was focused on eyebrow growth and did not report on scalp hair growth.[8] Other articles combined anti-inflammatory regimens or did not report concomitant treatment. Two retrospective studies provided objective assessment by trichoscopy or global photo assessment.[10,11] Among them, Vañó-Galván et al carried out the largest retrospective study with 51 patients diagnosed with LPP. All patients were on 0.25 mg-1mg of LDOM, while some were also on HCQ 200 mg or topical steroids. Results showed improved hair thickness in 39% (20 pts), stable disease in 53% (27 pts), and 8% (4 pts) had progressive hair loss.[10] Of the studies that reported a response timeline, treatment responses were observed within three to four months of treatment initiation and continued throughout the treatment period of 6–12 months.[7,8,10,11]

LDOM was well-tolerated with few side effects. However, one case reported pleural and pericardial effusion, as well as anasarca of an otherwise healthy patient with FFA after 3 weeks of daily 0.25 mg minoxidil treatment, which was resolved with discontinuation of OM and initiation of diuretics.[14] The patient was hospitalized and remaining side effects were mild and managed outpatient.

Concurrent hair loss conditions, such as androgenetic alopecia, were not explicitly described. In seven out of nine cases, minoxidil was used in combination with other standard treatments such as topical steroids, triamcinolone acetonide injections, various anti-inflammatory agents, 5-a-dihydrotestosterone inhibitors, etc.

Topical Minoxidil

Given the longer history of TM as a treatment for hair loss as compared to LDOM, it is better studied as a therapy for scarring hair loss.

Nineteen studies with 432 patients used TM as a treatment for CCCA, FFA, LPP, or TA (Table 2). The vast majority of patients were female, between 30 to 70 years of age. Less than 20 male

TABLE 1.

Summary of Studies Including the Use of Oral Minoxidil in Scarring Hair Loss

Disease	Author, Year	Study Design	Cohort	Regimen (mg/day)	Results	Adverse Effects	Concomitant Treatment	Note
CCCA	Lobon, 2021	Case report	N=1 F, 30yo	0.45-1	Hair regrowth after 4 months of treatment on clinical exam	Not reported	Bicalutamide 10-20mg/day, topical steroid*	--
FFA	Dlova, 2022	Case report	N=1 F, 40yo	0.25	Not reported	Pleural/pericardial effusion, anasarca after 3 weeks	Doxycycline 100 mg bid, TM 5%, tacrolimus 0.1%, topical steroid	Healthy patient prior to treatment. Adverse effects resolved with discontinuation of OM and diuretic treatment
FFA	Pirmez, 2020	Case series	N=7 F, 35-65yo	0.5-2.5	Regrowth of eyebrows (partial in 5, complete in 2 pts) after 6 months based on clinical photographs	Not reported	None	--
FFA	Huerth, 2020	Case report	N=1 F, 53yo	5.0	Disease progressed on clinical exam	Not reported	ILK (10mg/mL), topical steroid*, HCQ 400 mg/day	--
FFA	Cranwell, 2016	Case report	N=1 F, 46 yo	1.0	Disease stabilization on clinical exam	Not reported	Dutasteride 0.5mg/day; naproxen 1000mg/day HCQ 400mg/day, MTX 20mg/week for rheumatoid arthritis were continued with OM	Previous treatment with ILK with no benefit. Artificial hair transplant 3 years after disease stabilization (removed 12 months after due to folliculitis)
LPP	Gallo et al, 2022	Retrospective	N=12 F, 40-60yo	0.5	Hair thickness improved in global photo assessment and trichoscopy for all pts starting at 3 months, improvement through 12 months	Hypertrichosis (mild)	Anti-inflammatory agents (not specified)	--
LPP	Vañó-Galván, 2022	Retrospective	N=51 (36 F) mean 55yo	0.25-1	Hair thickness improved in 39% (20 pts), stable in 53% (27 pts), worsened in 8% (4 pts) of mean duration of 21 months (clinical and trichoscopy)	Hypertrichosis (n = 14), postural hypotension (n = 3), tachycardia (n = 2), and weight gain (n = 1).	HCQ 200 mg/day and, topical steroid in some pts	Diffuse LPP with better response (vs patchy). Higher doses OM with better response in male. LDOM was discontinued in 1 patient with tachycardia.
LPP, FFA CCCA, TA	Beach, 2021	Retrospective case series	N=17 (mean age M=33 yo, F=46yo	1.25-2.5	Increased scalp hair growth and decreased hair shedding	Lightheadedness, palpitations, ankle edema, hair shedding, hypertrichosis, urticaria, paresthesia	5α-reductase antagonists or other antiandrogen therapy, spironolactone, methotrexate, hydroxychloroquine, pioglitazone, platelet-rich plasma, doxycycline, retinoids	4 F patients had CCCA and TA; 2 F patients had AGA and LPP/FFA
FFA, TA	Beach, 2018	Case series	N=6 F, mean age 37 yo	1.25	Six of 18 patients (33%) reported decreased hair shedding, while five patients (28%) reported increased scalp hair (5/18)	Hypertrichosis, hypotensive symptoms, ankle edema	Not reported	--

CCCA, central centrifugal cicatricial alopecia; F, female; M, male; FFA, frontal fibrosing alopecia; OM, oral minoxidil; pts, patients; ILK, intralesional triamcinolone (Kenalog) injection; HCQ, hydroxychloroquine; LPP, lichen planopilaris; MTX, methotrexate; TA, traction alopecia
*Topical steroids were class I strength in all studies summarized in this table

TABLE 2.

Summary of Studies Including the Use of Topical Minoxidil in Scarring Hair Loss

Disease	Author, Year	Study Design	Cohort	Regimen (%)	Results	Adverse Effects	Concomitant Treatment	Note
CCCA	Eginli, 2017	Retrospective	N=9, F	Not specified	No statistically different change of severity score in TM vs. no treatment	Not reported	ILK, topical steroid*	--
CCCA	Callender, 2014	Case series	N=2, F, 25, 45yo	5%	Continued hair growth after hair transplant, improved pruritus	Not reported	ILK (5mg/mL) q3-4m topical steroids	Seborrheic dermatitis in one pt; Previously treated with topical steroids, ILK with no benefit
FFA	Cuenca-Barrales, 2021	Case report	N=1, F, 62yo	5% solution	Disease stabilization at 3 months	Not reported	Topical steroid	--
FFA	Batra, 2020	Case report	N=1, F, 45yo	5% solution BID	Decreased glabella-to hairline distance, hair and eyebrows regrowth, resolution of hyperkeratosis and redness	Not reported	FNS 5mg/day, HCQ 400mg/day, ILK (2.5mg/mL)	--
FFA	Ormaechea-Pérez, 2016	Case series	N=4, M mean 70yo	5% qhs	Disease stabilization	Not reported	Topical steroid	AGA all pts
FFA	Tosti, 2005	Case series	N=8, F 54-69yo	2% bid	Disease stabilization 50% (4 pts)	Not reported	FNS in 4 pts	Disease progressed on systemic glucocorticoid prior
FFA	Vañó-Galván, 2014	Retrospective	N=335 (343 F 12 M)	Not specified	Variable results depending on the associated systemic treatment	Not reported	Not specified	--
FFA	Jimenez, 2013	Case report	N=2, F, 58, 70yo	Not specified	10% graft uptake growth 4 years after hair transplant	Not reported	Not specified	Topical steroids, ILK, FNS 2.5 mg/day before transplant
FFA	Chen, 2012	Case report	N=1, M, 66yo	5% solution	Disease stabilization and resolution of inflammation in 6 months	Not reported	Not specified	Prednisone (1mg/kg, 2 weeks), topical steroids before TM
FFA	Tyagi, 2010	Case series	N=6, (5 F), 15-30yo	5% solution	70% graft uptake 6 months after hair transplant	None	Not specified	TM started after transplant
FFA	Tan, 2008	Case series	N=2, F, 40, 62yo	Not specified	Disease stabilization	Not reported	ILK	--
FFA	Cevasco, 2007	Case series	N=14	Not specified	Condition worsened in 3pts, moderate response in 5 pts good in 3 pts in TM monotherapy: moderate in 2 pts with combination	Not reported	ILK, topical steroid, and ketoconazole shampoo in 2 pts	Regrowth of hair, symptoms reduction, stabilization of disease assessed
FFA	Moreno-Ramírez, 2005	Case series	N=7, F mean 67yo	5% bid	Disease stabilization after 24 months	Not reported	Not specified	AGA all pts
FFA	Naz, 2003	Case report	N=1, F, 43yo	2% bid	No improvement after 6 months	Not reported	None	--
LPP	Mofarrah, 2020	Case report	N=1, F, 37yo	5%	Hair growth in AA**, improved hyperkeratosis and erythema after 3 months	Not reported	Prednisolone, HCQ, azathioprine, and levothyroxine for lupus and hypothyroidism were continued with TM	AA
LPP	Batra, 2020	Case report	N=1, M, 27yo	5% solution bid	Reduced visibility of the scalp, regrowth of vertex and crown hair, resolution of pruritus after 4 months	Not reported	Topical steroid, tofacitinib 10mg/day, dapsone	Previous treatment with ILK, HCQ, MMF, acitretin, naltrexone no benefit
LPP	Saxena, 2016	Case report	N=1, M, 24yo	5% bid	80% graft uptake 10 months after transplant, improved scar quality	Not reported	None	TM started after transplant
LPP, FFA (17, 15 pts)	Mardones, 2017	Retrospective	N=32 (31 F, 1 M)	2-5% lotion	Mild improvement in 65% (49 pts) and 74% (20 pts); progressed in 35% (26 pts), 26% (7 pts) in LPP and FFA after 12 months***	Not reported	Topical steroid, cetirizine 5mg/day in all pts, salicylic acid 1% lotion, HCQ 200-400mg/day, FNS 1-2.5mg/day, MTX 7.5-15mg/week, isotretinoin in some pts	One male with Graham–Little–Piccardi–Lassueur syndrome
LPP	Kossard, 1997	Case series	N=2	2%	No evident benefit	Not reported	Not specified	--
TA	Khumalo, 2006	Case series	N=2, F, 45, 54yo	2% bid	Hair growth starting in 3 months, improving through 6-9 months	Not reported	Not specified	--

AA, alopecia areata; CCCA, central centrifugal cicatricial alopecia; F, female; M, male; FFA, frontal fibrosing alopecia; TM, topical minoxidil pts, patients; ILK, intralesional triamcinolone (Kenalog) injection; HCQ, hydroxychloroquine; LPP, lichen planopilaris; MMF, micophenolate mofetil; MTX, methotrexate; TA, traction alopecia

*Class I topical steroid in all study in this table

**AA and LPP developed same time

***pts were treated with multiple regimen, and study does not reveal who had minoxidil among 32 pts

patients were included in these studies. Among articles with available data, 2-5% topical minoxidil was used in various forms such as solution or foam once to twice daily. Fourteen studies reported positive results such as disease stabilization, regrowth of hair, etc. Improvement of symptoms such as pruritus, and hyperkeratosis was reported as well.[15-28] Six studies reported no improvement or worsening of the conditions.[25,28-32] Mardones et al comprehensively reported mild improvement in about 70% and progression in about 30% of patients after 12 months of 2-5% topical minoxidil treatment for 32 LPP and FFA patients.[25] Among the literature that reported response timelines, treatment responses were observed starting at month three of treatment and continued throughout the treatment period of up to 24 months.[16,17,20-22,24,25,33]

TM was extremely well-tolerated with no reported side effects. Common secondary diseases, such as androgenetic alopecia and seborrheic dermatitis were reported in at least four studies.[15,18,21,22]

In most cases, similar to LDOM, TM was used with other standard treatments. Two cases reported TM monotherapy. One study reported a benefit from monotherapy of LPP[23], while the other reported no improvement in FFA.[31]

DISCUSSION

TM and LDOM have been widely used for a variety of hair loss conditions, with efficacy demonstrated primarily in androgenetic alopecia.[3] With the limited knowledge regarding minoxidil treatment in scarring alopecia, this review carried out a comprehensive search of the current literature.

Both TM and LDOM studies on scarring alopecia were retrospective or case studies. The most frequently studied conditions were LPP and FFA, followed by CCCA. Among the available literature, LDOM demonstrated improvement or stability in disease in about 80 to 100% of cases with or without other treatment modalities.[10,11] TM was beneficial in approximately 70 to 100% of cases.[25,28] Positive responses were observed as early as 3 months after treatment in both LDOM and TM and continued throughout the treatment course in reported cases. Although LDOM and TM are comparable in efficacy, it has been suggested that there is better patient compliance with the oral form of minoxidil due to its convenience of use.[3] While our review does not provide head-to-head comparisons, this trend may also be true in the treatment of scarring alopecias. In the vast majority of cases reported, LDOM and TM were well-tolerated with minimal side effects.

Minoxidil has promising data as an effective and safe option for scarring alopecia conditions including CCCA, LPP, FFA, and TA. However, current data on minoxidil use in scarring alopecia has a few limitations. Only a few studies were available that studied a cohort of patients with an objective response measurement.[10,11] Studies were retrospective with small sample sizes and did not control for concomitant hair loss conditions and treatment effects. The descriptions of responses and timelines were heterogeneous, which hindered direct comparison between studies.

In several studies using human serum samples, mice, and cell culture, both in vivo or in vitro, mechanisms of action have been proposed regarding the effect of minoxidil. These include 1) stimulation of the blood circulation near hair follicles, 2) increased vascular endothelial growth factor expression and vascularization around the hair follicles, increasing oxygen and growth factor delivery, 3) activation of the prostaglandin-endoperoxide synthase one, 4) direct stimulation of the hair follicles by acting as an 'epidermal growth factor' on matrix cells, thus prolonging the duration of the anagen phase via the activation of the beta-catenin pathway.[34,35] Other actions of minoxidil specifically for scarring hair loss conditions may be its demonstrated anti-fibrotic properties.[35] Minoxidil may also downregulate pro-inflammatory cytokine interleukin-1 alpha gene expression with a possible anti-inflammatory effect.[36] Minoxidil also moderates molecules in the activation process of T lymphocytes, having an immunomodulatory effect, with possible positive outcomes in autoimmune alopecia.[37]

In summary, several mechanisms of minoxidil may contribute to the improvement of non-scarring hair loss, as well as scarring alopecias. Current data on the effectiveness and safety of minoxidil use in scarring hair loss is promising. Well-designed retrospective and prospective studies with objective outcome measurements are needed.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.7894

March 2024 152 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Attenuation of Atopic Dermatitis in Newborns, Infants, and Children With Prescription Treatment and Ceramide-Containing Skin Care: A Systematic Literature Review and Consensus

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ABSTRACT

Background: Atopic dermatitis (AD) typically starts in infancy and early childhood. The chronic skin disorder is associated with recurrent flares, pruritus, and genetic predisposition. Daily use of moisturizers that contain lipids, such as ceramides, reduces the rate of AD flares and the need for topical steroid treatment. We aimed to provide insights on AD attenuation to tailor AD prescription therapy, skin care, and maintenance treatment to improve pediatric patients with AD and families.

Methods: A panel of 6 pediatric dermatologists and dermatologists who treat neonates, infants, and children developed a consensus paper on AD attenuation for pediatric patients. The modified Delphi process comprised a face-to-face panel meeting and online follow-up to discuss the systematic literature search results and draw from clinical experience and opinion of the panel to adopt and agree on 5 statements.

Results: Understanding the functional properties of newborn and infant skin, discussing skincare product use with parents, and recommending tailored prescription and skincare routines can improve newborn, infant, and children's skin health. Studies on the prophylactic application of moisturizers initiated in early infancy suggest moisturizers may delay rather than prevent AD, especially in high-risk populations and when used continuously. Increasingly there is evidence that moisturizer application reduces the severity of AD and extends the time to flares, which may help attenuate the atopic march. The protective effect of skin care for AD has been observed in studies where its daily use is ongoing; these beneficial effects may be lost in less than 1 year after cessation. It is therefore important to emphasize that skin care should be routinely used when counseling patients and caregivers.

Conclusion: Healthcare providers can improve patient outcomes in atopic-prone infants and children by providing instructions regarding the daily benefits of applying skin care with gentle cleansers and moisturizers. Using gentle cleansers and moisturizers containing barrier lipids from birth onward may delay AD occurrence and mitigate severity in predisposed infants.

J Drugs Dermatol. 2024;23(3):152-159. doi:10.36849/JDD.7894

INTRODUCTION

Atopic dermatitis (AD) is a common recurrent cutaneous disorder associated with pruritus and genetic predisposition that typically begins in infancy and early childhood.[1] It is unclear if AD is a single disease entity or a spectrum of diseases with a shared phenotype.[1-5] Certain clinical features are highly characteristic of AD, such as morphology, anatomic distribution, marked pruritus, relapsing course and or seasonal variation, associated xerosis, and a personal or family history of atopy.[1-5] Maintaining a healthy skin barrier starting early in life, using daily and ongoing skin care with a gentle cleanser and a lipid-containing moisturizer has been shown to reduce the number of flares and reduce AD severity.[6-8] However, evidence on interventions to prevent AD in pediatric patients is conflicting.

This consensus paper aims to provide insights into the literature about AD attenuation in newborns, infants, and children. We further explore gentle cleansers and moisturizers, particularly ceramide-containing skin care, offering insights into their specific role in attenuating AD as monotherapy or as an adjunct to AD treatment for the pediatric population.

MATERIALS AND METHODS

The consensus project used a modified Delphi process comprising face-to-face (February 10, 2023) discussions followed-up online.[9] The process entailed preparing the project, selecting the panel, and conducting systematic literature searches to inform 15 draft statements.[9] During the meeting, the panel evaluated the draft statements during a workshop. Then, a plenary discussion adopted 5 statements to provide clinical data for pediatric dermatologists, dermatologists, and pediatric healthcare providers.

Systematic Literature Searches

The scope of the literature search comprises the attenuation of AD for newborns, infants, and children and the role of skin care, such as ceramide-containing skin care as a monotherapy or as an adjunct to prescription topical and systemic medication.

The literature review considered clinically relevant materials published in English between January 2010 and December 20, 2022, including randomized controlled trials, other clinical studies, guidelines, consensus papers, and review articles. Systematic literature searches on PubMed and Google Scholar (secondary source) were conducted on December 20-22, 2022, by a researcher/clinician (HA) and a physician/scientist (AA).

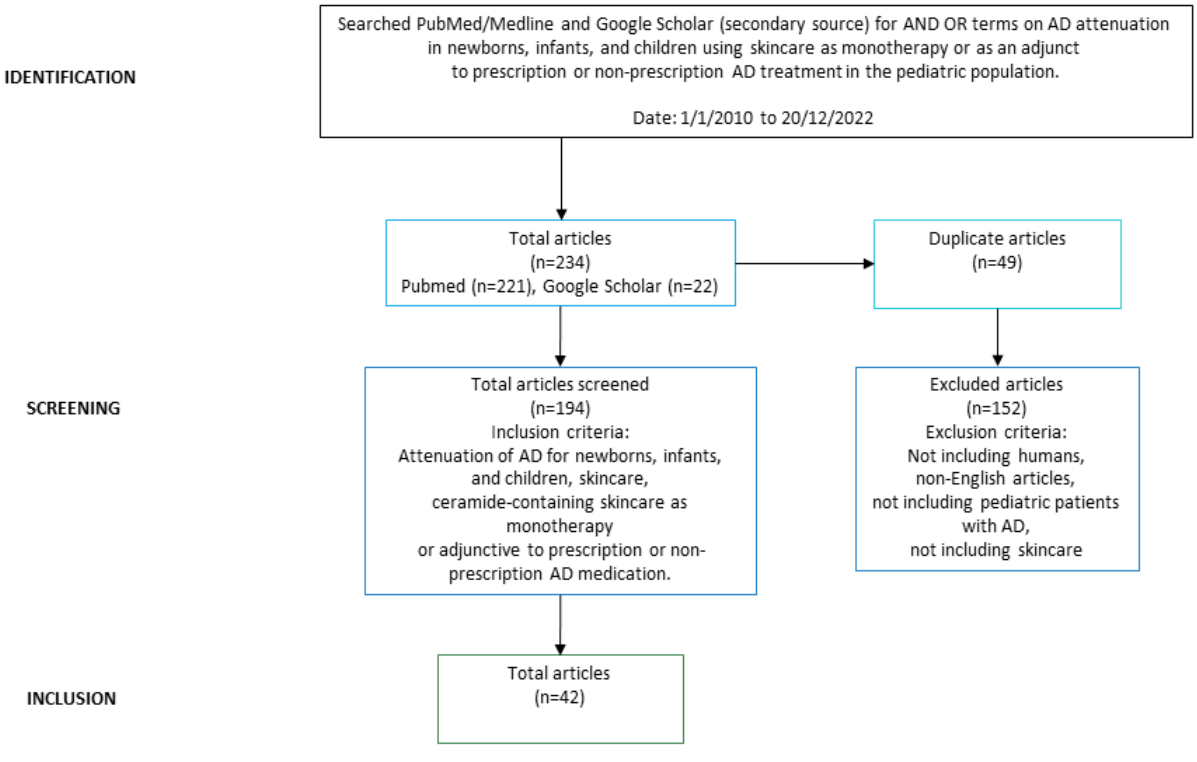
Search terms are provided in Table 1. First, titles and abstracts were reviewed, followed by the full article. The 2 reviewers evaluated results independently, and selected publications were graded based on reviewer consensus. Each selected clinical publication that included skincare information was graded (A, B, or C for study type and 1-4 for likelihood to change confidence in the effect shown).[9]

TABLE 1.

Search Terms: 2 Groups	
Search Terms – Group 1	**Search Terms – Group 2**
Atopic dermatitis AND	Atopic dermatitis AND
neonates OR	neonates OR
infants OR	infants OR
children AND	children AND
atopic march OR	prescription OR
pathogenesis OR	adjunctive OR
guidelines OR	skin care OR
algorithms OR	moisturizer OR
consensus OR	emollient OR
prevention OR	ceramide OR
attenuation OR	skin maturation and moisturization
treatment OR	--
maintenance	--

The 194 studies that met the quality criteria of the literature search informed the creation of 15 draft messaging statements to guide the development of a manuscript. After the panel discussions and online follow-up, a further 152 articles were excluded, leaving n=42 (Figure 1).

FIGURE 1. Systematic literature search results.



RESULTS

Statement 1

Studies have shown that AD-affected skin demonstrated stratum corneum (SC) barrier dysfunction and decreased ceramides and free fatty acid levels. Even the intact skin of a patient with AD that is not flaring is compromised and has impaired barrier function.

AD is characterized by compromised epidermal barrier integrity.[1-5,10]

Research suggests that defects in the skin barrier may be a critical factor in initiating infantile AD and other allergic diseases.[11-13] It has been determined that even the intact, non-flaring skin of a patient with AD is compromised with an impaired barrier function.[1-5] Barrier dysfunction causes a decrease in SC cell adhesion and increased inflammation.[14] The ability of the skin to retain water is decreased, which leads to a cycle of xerosis and itching, scratching, damaged skin, and inflammation.

Filaggrin (FLG) is a filament-binding protein that is essential to the development of the skin barrier and the maintenance of epidermal homeostasis.[15,16] Loss-of-function gene mutations for FLG are a significant risk factor for AD.[16] Clinical studies have identified a relationship between FLG loss-of-function mutations or downregulation, increased transepidermal water loss (TEWL), and infant AD development.[17-19] In a prospective cohort study in 1836 infants, Hoyer et al found an association between FLG loss-of-function mutations (n=166) and the presence of AD at age 3 months (OR 2.89, 95% CI, 1.95-4.28; *P*< .001).[19] Significantly higher TEWL was also observed in the mutation carriers at 6 months (mean 9.68 [95% CI 8.69-10.68]) vs noncarriers (8.24 [95% CI, 7.97-8.15]; *P*<.01).

AD has also been associated with abnormal SC lipid levels, which disrupts lamellar matrices, diminishes skin barrier function, and increases dermal sensitivity to allergens and irritants.[20] Ceramides, in particular, are lipids essential in forming the waterproof barrier of the SC, thereby retaining water in the skin and reducing TEWL.[10] The chain length of very long fatty acids within ceramides is necessary for proper barrier function. Lower levels of longer-chain ceramides and higher levels of shorter-chain ceramides have been found to be expressed in the skin of patients with AD compared to healthy individuals.

Statement 2

As recommended in international guidelines, daily moisturization is an integral part of AD management. Gentle cleansers and moisturizers may improve skin barrier function in AD and reduce skin susceptibility to irritants and xerosis.

Evidence-based international guidelines recommend daily moisturization to treat skin barrier dysfunction and hydrate skin, which is the foundation of AD management.[22-27] According to the US, Canadian, and European guidelines, moisturizers are integral to monotherapy, adjunctive, preventative, and maintenance treatment of AD.[22, 24-27] These guidelines generally support using moisturizers for skin hydration and AD symptom improvement as the primary treatment for mild disease and in conjunction with other agents for moderate-to-severe disease (Table 2).[24]

In treating AD, restoring skin barrier function has long been a therapeutic goal; evidence demonstrating the success of topical moisturizers in these efforts is accumulating. In a double-blind, randomized, vehicle-controlled trial, Boralevi et al investigated the effects of long-term moisturizer therapy on AD-associated xerosis in young children (n=251, age 2-6 years).[6] During a 28-day period, the objective SCORAD score, xerosis score of the SCORAD index, and visual analogue score decreased, and skin hydration increased more in participants in the moisturizer group (n=124) than in the vehicle group (n=125, *P*<.001 for all measures).

Hebert et al conducted a systematic review of clinical trials published between 2006 and 2019 that assessed the treatment of AD with daily moisturization.[23] Studies included in the systematic review evaluated the efficacy of various commercially available moisturizers using endpoints such as TEWL, corneometry, or incidence of flare. These studies showed that moisturizers (typically applied twice daily) significantly improved skin barrier function in children and adults with AD. Studies that conducted side-by-side (split body) comparisons demonstrated that skin barrier integrity was improved with moisturization vs no treatment in nearly all cases (Table 3).

Danby et al performed a randomized, observer-blinded, intra-patient-controlled study investigating a test cream containing triglycerides, ceramides, and cholesterol in a multivesicular emulsion vs a paraffin-based emollient without physiological skin lipids in adults with dry AD-prone skin.[20] Skin areas on the forearm and lower leg treated with the test cream demonstrated a greater increase in skin barrier integrity (effect size for area under the TEWL curve -162, 95% CI, -206 to -118) than that observed with the reference cream. The test cream also reduced TEWL (-15.3 g/m2/h, 95% CI -20.3 to -10.4) and skin sensitivity to sodium lauryl sulfate (-0.5 points visible redness, 97.57% CI, -1.00 to -0.25) compared to the reference cream. Furthermore, lipid chain order was enhanced and associated with skin barrier integrity (r = 0.61) in areas of skin treated with the test cream. The test cream also decreased signs of dryness and increased hydration (8.61 capacitance units, 95% CI, 6.61–10.6) compared to the reference. The investigators concluded that the test cream containing triglycerides, ceramides, and cholesterol facilitated skin barrier restoration and protection from irritation and dryness superior to the paraffin-based reference.

Danby et al also conducted a double-blind, intra-participant, vehicle-controlled study to evaluate the benefits of a test cream and lotion containing ceramides in a multivesicular emulsion for dry skin.[28] Adults with dry, AD-prone skin applied 100 µl of the test lotion or test cream, 3 paraffin-based reference creams (Zerobase, Epimax, or Aquamax), or nothing (control) on 6 treatment sites on the lower leg. Visual dryness and skin hydration scoring were measured at timed intervals (3, 6, 12, and 24 hours after product application). A single application of the ceramide-containing test cream and test lotion increased hydration significantly ($P<.001$) and reduced skin dryness ($P<.05$) for 24 hours compared to the control site. The test cream and lotion were the only products tested that sustained clinically meaningful improvements in skin moisturization for 24 hours, reducing the burden of frequently applying moisturizers in managing xerosis in conditions such as AD.

The application of moisturizers is recommended as an integral part of AD prevention, treatment, and maintenance. However, selecting an inappropriate skincare product may be irritating or even worse, cause additional damage to and depletion of dermal intercellular lipids, exacerbating xerosis.[10] Therapeutic moisturizers developed specifically for treating AD symptoms have demonstrated improved skin barrier, reduced susceptibility to irritants, and a decreased incidence of flares in clinical trials.[6-8,11,13,23,29-32] These moisturizers are gentle, non-alkaline, and are specifically formulated to restore the skin barrier, often with physiologic skin lipids, such as ceramides, that maintain and support the skin barrier.[33]

Statement 3

Studies showed that the prophylactic application of moisturizers initiated in early infancy might delay rather than prevent AD

TABLE 2.

Guidelines and Algorithms			
Author/Year	**Type of Patients/ Disease**	**What Was Recommended**	**Key Findings**
Wollenberg A, et al/2018[22]	Adults and children with AD	Frequent, liberal use of emollients should be prescribed as basic therapy for adults and children with AD Emollient soap substitutes and bath oils should be used Emollients with a higher lipid content are preferred during the winter season In mild-to-moderate AD, regular use of emollients has a long- and short-term steroid-sparing effect after AD remission achieved with topical prescription medications	Certain moisturizers improve skin barrier function in AD and protect against irritants Emollients are "the mainstay of management" of AD
Eichenfield LF, et al/2014[24]	Patients with AD	Moisturizers should be used alone, adjunctively, and for prevention and maintenance in AD Moisturizers should be applied soon after bathing and up to TID	Moisturizer monotherapy is appropriate for mild AD Adjunctive use of moisturizers is appropriate for moderate-to-severe AD Moisturizers are important for maintenance treatment and flare prevention in AD
Wollenberg A, et al/2018[25]	Adults and children with AD	Emollients should be prescribed as basic therapy for adults and children with AD	Adjunctive daily use of emollients should be combined with dupilumab treatment
Lansang P, et al/2019[26]	Children with AD	Regular application of emollients should be part of basic daily care Emollients should be applied immediately after daily bathing to maintain skin barrier	AD is a chronic disease that requires ongoing skin care to maintain the skin barrier and prevent flares Early daily application of emollients may reduce or delay the development of AD in high-risk infants
Le Poidevin LM, et al/2019[27]	Patients with AD	Large amounts of moisturizers should be applied BID or TID 2 international guidelines recommend moisturizers with specific ingredients (ie, petrolatum, ceramides, or glycerol)	There was a consensus among 14 international guidelines on the benefits of moisturizer use in AD, even on skin without lesions
Schachner L, et al/2021[33]	Neonates and infants with 3 clinical signs: xerosis, erythema, or erosion/bulla	Monotherapy and adjunctive skin care recommended CER-containing moisturizers are preferred	Non-alkaline cleansers and CER-containing moisturizers used daily maintain a healthy skin barrier and reduce inflammation Gentle moisturizers and cleansers containing barrier lipids help maintain the protective skin barrier when applied from birth onward

Atopic dermatitis (AD), Ceramide-containing moisturizer (CER), 3 times a day (TID), Twice a day (BID)

(moderate certainty), especially in high-risk populations and when used continuously.

Daily use of emollient therapy from birth to enhance skin barrier function may significantly delay the onset of AD in high-risk infants.[11-13,23,26] However, there is some evidence that this treatment may delay rather than prevent AD. Even in the absence of active disease, the chronic nature of AD requires ongoing basic care to maintain the skin barrier.[23,26]

A systematic review and meta-analysis by Zhong et al investigated the efficacy and safety of prophylactic emollients initiated during the first 6 weeks of infancy to prevent AD and food allergies.[34] The review identified randomized controlled trials published between January 2000 and July 2020 that evaluated the effect of prophylactic emollients within the first 6 weeks of life vs no treatment on AD development by 2 years of age. There was no significant reduction in AD development (RR 0.84, 95% CI, 0.64, 1.10) compared to the control group in the 10 studies that fulfilled the inclusion criteria. However, prophylactic moisturizers exhibited an improved skin condition (RR 0.75, 95% CI 0.62-1.11) in infants at high risk for AD development (n = 8 studies). A significant benefit (RR 0.59, 95% CI 0.43, 0.81) was also identified in studies (n = 6) in which emollients were used continuously until AD assessment; however, this effect was not observed if treatment had been interrupted prior to that time. The authors concluded that the application of emollients initiated during the first 6 weeks of infancy — particularly in high-risk populations and with continuous use may delay rather than prevent AD.

Statement 4

Moisturizer use benefits young AD patients, reducing the severity and extending the time to flares. This could help prevent or attenuate the atopic march.

An inhibited barrier function in AD may result in periodic flare-ups of erythematous and pruritic lesions; therefore, delaying or preventing flares is key in managing this disease. AD treatment guidelines recommend daily treatment of atopic skin with moisturizers to prevent flares and maintain a flare-free state.[24,26,27] Van Zuuren et al conducted a systematic review of randomized controlled trials that enrolled people with AD.[29] The review included 77 studies (N=6603; age 4 months to 84 years [mean 18.6 years]; mean treatment duration, 6.7 weeks). When all moisturizers were compared to vehicle, placebo, or no moisturizer, they were found to produce fewer flares (6 studies, n=607; RR 0.33, 95% CI, 0.17 to 0.62; moderate-quality evidence) and lower investigator-assessed disease severity scores (12 studies, n=1281; SMD -1.04, 95% CI,-1.57 to -0.51; high-quality evidence).

In addition, moisturizer combined with active topical treatment was more effective in reducing flares (1 study, n=105; RR 0.43, 95% CI, 0.20 to 0.93; low-quality evidence) and in lowering investigator-assessed disease severity (3 studies, n=192; SMD-0.87, 95% CI, -1.17 to -0.57; moderate-quality evidence) than the active treatment alone. The authors concluded that most moisturizers produce some beneficial effects, prolong time to and decrease the number of flares, and reduce the number of topical steroids needed to diminish eczema severity.

TABLE 3.

Meta-analyses			
Author/Year	**Type of Patients/ Disease**	**What Was Recommended**	**Key Findings**
Van Zuuren EJ, et al/2017[29]	6603 patients with AD, age 4 mo-84 y (mean 18.6 y)	Most moisturizers had some beneficial effects, such as: - prolonging time to AD flares -decreasing number of AD flares - reducing amount of topical steroid needed to reduce AD severity	Compared to vehicle, placebo, or no moisturizer, moisturizers produced: - fewer flares (6 studies, n=607; RR 0.33, 95% CI, 0.17 to 0.62) - lower investigator- assessed disease severity scores (12 studies, n=1281; SMD -1.04, 95% CI, -1.57 to -0.51) - fewer flares when combined with active topical treatment (1 study, n=105; RR 0.43, 95% CI, 0.20 to 0.93) - lower investigator-assessed disease severity scores than active topical treatment alone (3 studies, n=192; SMD -0.87, 95% CI, -1.17 to -0.57)
Zhong Y, et al/2022[34]	3409 infants at high or normal risk for the development of AD	Emollients initiated during first 6 weeks of infancy may prevent AD—particularly in high-risk populations and with continuous use Emollients may delay rather than prevent AD	Emollient use initiated during first 6 wks of infancy did not significantly reduce AD development at 2 yo compared to control (RR 0.84, 95% CI, 0.64, 1.10) Prophylactic moisturizers exhibited a significant benefit (8 studies; RR 0.75, 95% CI 0.62-1.11) in infants at high risk for AD development A significant benefit (6 studies; RR 0.59, 95% CI 0.43, 0.81) was identified when emollients were used continuously until AD assessment at 2 yo; t his effect was not observed if treatment had been interrupted

Atopic dermatitis (AD), Standard mean deviation (SMD), Years of age (yo)

TABLE 4.

Randomized Controlled Trials, Including Skin Care			
Author/Year	**N**	**What Was Studied**	**Key Findings**
Boralevi F, et al/2014[6]	251/children with AD, age 6-12	Effect of moisturizer (n=124) or vehicle (n=125) applied at least QD on AD-associated xerosis	After the 28-day, double-blind period, children receiving moisturizer had a lower objective SCORAD score and decrease in xerosis score than at baseline vs vehicle (66.1% vs 45.6%, respectively; P<.001)
Weber TM, et al/2015[7]	45/infants and children with AD (mean age 3.5 y)	Effect of QD moisturizer and cleanser (n=21) or cleanser only (n=24) applied for 6 mos or until flare	Flare incidence lower in moisturizer + cleanser vs cleanser only group (21% vs 65%; P=.006)
Ma L, et al/2017[8]	64/children with mild-to-moderate AD (age 2-12 y)	Effect of QD CER-containing body wash and BID moisturizer (n=32), or only QD CER-containing body wash (n=32) for 12 wks on flare	Body wash + moisturizer group had nearly 2 mos delay in median time to flare (89 vs. 27 days), earlier onset of action re: fewer flares at wk 4 (31% vs 59%, P = .022), and fewer flares at 12 wks (50% vs 72%, P=.079) vs body wash alone
McClanahan D, et al/2019[11]	100/neonates at high-risk for AD	Development of AD at 12 mo or 2 y after applying QD CER + filaggrin-associated AA-containing emollient (n=54) or emollient of choice (n=46)	AD diagnosed at 12 mos in 13.2% vs 25% (P=.204) and at 2 y in 19.4% vs 31% (P=.296) of participants in each group, respectively; trend in favor of the CER + AA group
Horimukai K, et al/2014[12]	118/neonates at high-risk for AD	Development of AD at 32 wks after QD application of emollient moisturizer (n=59) or petroleum jelly control (n=59)	32% fewer neonates in the emollient group developed AD vs the control group (P = .012, log-rank test)
Simpson EL, et al/2014[13]	124/neonates at high-risk for AD	Development of AD at 6 mos after at least QD application of emollient (n=64) vs no emollient (n=60)	Relative risk reduction of 50% (RR 0.50, 95% CI, 0.28-0.9; P = .017) in the cumulative incidence of AD at 6 mos observed in the emollient group
Chaoimh CN, et al/2022[39]	321/infants at high risk for AD	Effect of BID oat-, fatty acid-, and CER-containing emollient for first 8 wks of life (n=161) vs standard routine skin care (n=160)	Cumulative incidence of AD in the emollient group at 12 mos was 32.8% vs 46.4% in the standard routine skincare group (RR 0.707, 95% CI, 0.516, 0.965; P = .036); early application of an emollient for very dry, AD-prone skin reduced AD incidence in 1 yo high-risk infants
Chalmers JR, et al/2020[41]	1394/neonates at high risk for AD	Effect of at least QD emollient (n=693) or mild cleansers/shampoos (control group, n=701) on incidence of AD at 2 yo	At 2 yo, AD was present in 23% of participants with evaluable data in the emollient group (n=598) and 25% of such infants in the control group (n=612, adjusted RR 0.95, 95% CI, 0.78 to 1.16; P = 0·61; adjusted risk difference -1·2%, -5.9 to 3.6)
Skjerven HO, et al/2020[42]	2397/neonates not selected for atopy	Effect of skin intervention (bath + added oil and face cream applied from age 2 weeks), food intervention (eggs, wheat, cow's milk, + peanut butter introduced between age 12-16 weeks), skin + food intervention, or no intervention (control group) on incidence of AD at age 12mo	At age 12 mos, incidence of AD was 11% in skin intervention group, 9% in food intervention group, 5% in combined intervention group, and 8% in control group (risk differences favored control group); incidence of AD was not reduced by skin or food interventions

Atopic dermatitis (AD), Once a day (QD), Years of age (yo), Months (mo)

A randomized controlled study in Chinese children (N=64, age 2-12 years) with mild-to-moderate AD enrolled participants within 1 week after successful treatment with a topical corticosteroid.[8] Patients were randomly assigned to a group that applied a ceramide-containing body wash and moisturizer once and twice daily, respectively (n=32), or only ceramide-containing body wash once daily (n=32) for 12 weeks. A delay in the median time to AD flare of nearly 2 months was shown for the group applying body wash and moisturizer compared to those using body wash alone (89 vs 27 days, respectively).[8]

A randomized controlled study, investigated the efficacy of 2 non-prescription, steroid-free skincare formulations in relieving the symptoms and reducing the risk of flare in infants and children with AD.[7] Following a 2-week washout period, participants (N=45; mean age 3.5 years [range 3 mos-12 y]) were randomized to apply either the cleanser only (control group) or the cleanser and a daily moisturizing body cream once daily for 6 months or until flaring. The cleanser contains mild surfactants and panthenol and the cream contains colloidal oatmeal, licochalcone A, and ceramide 3. Compared with the control group, the incidence of flaring was significantly lower in the moisturizer plus cleanser group (21% vs 65%; *P*=.006).

The consensus among medical practitioners is that a significant proportion of high-risk children will develop persistent cases of AD and/or other atopic diseases such as allergic rhinitis or asthma. A higher prevalence of rhinitis and asthma[35] or asthma[36] has been associated with more severe AD compared to milder disease. In an Italian cohort of patients with AD (followed 16.9 years on average), the risk of asthma onset increased 4 times in patients with severe AD compared to moderate AD and 2 times in patients with moderate AD compared to mild AD.[36] Data collected in retrospective and prospective cohort studies in patients with severe AD have shown similar results.[37,38] Based on these findings, the ability of moisturizers to help reduce the severity of AD and the incidence of flares in young patients could assist in attenuating atopic march.

Statement 5

When applied from birth onwards, gentle cleansers and moisturizers containing barrier lipids may mitigate AD occurrence and severity in predisposed infants.

A growing body of evidence supports skin care starting early in life, recognizing the benefits of ongoing daily use of non-alkaline cleansers and moisturizers to promote a healthy skin barrier (Table 4). When applied from birth onwards, gentle cleansers and moisturizers containing barrier lipids, like ceramides, help maintain the protective skin barrier and improve xerosis, possibly reducing the severity, delaying the occurrence, or preventing AD development in predisposed infants.[11-13,39,40]

Horimukai et al conducted a randomized, prospective, controlled trial to investigate whether applying a moisturizer during the neonatal period prevents the development of AD.[12] Neonates (n=118) at high risk for AD based on family history were enrolled in this study. During the first 32 weeks of life, an emulsion-type moisturizer (2e) was applied daily to the treatment group (n=59). Study results indicated that 32% fewer neonates receiving the emulsion-type moisturizer had developed AD at week 32 compared to the participants receiving the petroleum jelly control (n=59; *P*=.012, log-rank test). The investigators concluded that daily applying an emollient-type moisturizer decreases the risk of AD in infants during the first 32 weeks of life.

Simpson et al performed a randomized controlled trial in the US and the United Kingdom in neonates (N=124) determined to be at high risk for AD.[13] Starting within 3 weeks of birth, parents in the intervention arm applied full-body emollient therapy (in the UK, sunflower seed oil, Doublebase Gel, or liquid paraffin 50%; in the US, sunflower seed oil, Cetaphil Cream or Aquaphor Healing Ointment) to the neonates (n=64) at least once daily, whereas parents of the neonates in the control arm (n=60) did not apply emollients. This study identified a statistically significant protective effect in the neonates who received daily full-body emollient. In addition, a relative risk reduction of 50% (RR 0.50, 95% CI, 0.28-0.9; *P*=.017) on the cumulative incidence of AD was observed in this group. The investigators concluded that emollient therapy from birth is an effective approach for preventing AD; however, they suggested that this effect needs to be confirmed in larger trials.

Chaoimh et al conducted a randomized controlled clinical trial that investigated the incidence of AD at 12 months in high-risk infants in which emollient was applied daily from birth to 2 months.[39] Infants were identified as high risk for AD based on parental history of AD, asthma, or allergic rhinitis. The newborns were enrolled in the study within 4 days of birth and were randomly assigned to receive either an emollient (containing oat ingredients, ceramides, and fatty acids) specifically formulated for very dry, AD-prone skin twice daily for the first 8 weeks of life (intervention group, n=161), or to standard routine skin care (control group, n=160). In the intervention group, the cumulative incidence of AD at 12 months was 32.8% vs 46.4% in the control group (RR 0.707, 95% CI, 0.516, 0.965; *P*=.036). The investigators concluded that the early application of an emollient specifically formulated for very dry, AD-prone skin until 2 months of age reduces the incidence of AD in high-risk infants at 1 year of age.

McClanahan et al conducted a randomized controlled trial enrolling neonates (n=100) at high risk for AD development based on family history.[11] The intervention group received a once-daily full-body application of a ceramide and FLG-associated amino acid-containing emollient. The control arm used a full-body application of an emollient of their choice for dry skin but was requested not to apply it regularly. In the intervention and the control groups, AD was diagnosed in 13.2% vs 25.0% of the participants at 12 months (*P*=0.204) and 19.4% vs 31.0% at 2 years (*P*=0.296), respectively. Although a favorable trend was observed in the intervention group, it was not statistically significant, possibly because of a lack of power due to under-enrollment. The investigators concluded that the trends observed in this study suggest a protective effect of daily full-body therapy with the study emollient compared to the control.

The results of these studies on the prophylactic application of moisturizers for the prevention of AD in infants demonstrate positive trends, but conclusive evidence is lacking.[12,13,40] A large-scale, randomized controlled study by Chalmers et al in neonates (N=1394) at high risk of developing AD (based on having at least 1 first-degree relative diagnosed with AD, asthma, or allergic rhinitis) failed to confirm these results.[41] Newborns assigned to the intervention group (n=693) received emollient (Doublebase Gel or Diprobase Cream) applied at least once daily, and the control group (n=701) was treated with just mild cleansers or shampoos. The results of this study indicated that at age 2 years, AD was present in 23% of infants with evaluable data in the emollient group (n=598) and 25% of such infants in the control group (n=612; adjusted RR 0.95, 95% CI, 0.78 to 1.16; *P*=0·61; adjusted risk difference -1·2%, -5.9 to 3.6). The authors concluded that the study results provided "no evidence that daily emollient during the first year of life prevents eczema in high-risk children." However, it should be noted that study results were partly based on parent- and patient-reported secondary outcome measures rather than objective ascertainment. These included the parental report of clinical diagnosis/time to onset of AD, parent completion of UK Working Party criteria, and patient-reported severity of eczema.

Skjerven et al conducted a randomized controlled trial that included newborns (N=2397) who were not selected according to atopy.[42] The newborns were randomized at birth into 4 groups: skin intervention (bath with added oil and face cream applied from age 2 weeks), food intervention (eggs, wheat, cow's milk, and peanut butter introduced between age 12-16 weeks), skin + food intervention, or no intervention (control group). By

age 12 months, AD was observed in 11% of the infants in the skin intervention group, 9% in the food intervention group, 5% in the combined intervention group, and 8% in the control group (risk difference of 3.1%, 95% CI, -0.3 to 6.5 for the skin intervention and risk difference of 1.0%, 95% CI, -2.1 to 4.1 for the food intervention, in favor of the control group). The authors concluded that "neither skin emollients nor early complementary feeding reduced development of AD at 12 months."

While the results of the large-scale trials[41,42] may appear nonconfirmatory, it should be noted that using other moisturizer formulations may have produced a different effect.

CONCLUSION

Discussing and recommending optimized skincare products and routines to parents can help attenuate AD in newborn and infant skin. Healthcare providers can improve patient outcomes by providing instruction regarding the benefits of applying clinically tested therapeutic moisturizers daily to improve skin barrier function and help delay, reduce, or maybe prevent AD.[23] The protective effect of skin care for AD has been observed in studies where its daily use is ongoing;[34] these beneficial effects may be lost less than 1 year after cessation.[20] It is therefore important to emphasize that skin care should be routinely used, during and between flares, when counseling patients and caregivers.[26]

DISCLOSURES

CeraVe International supported the research for this work. The authors, LS, AA, LB, MG, LK, PL, GM, received fees for attending the meeting. The authors reviewed the manuscript and agreed with the final version and have no conflict of interest with the content of the manuscript.

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doi:10.36849/JDD.8138

March 2024 160 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Novel Systems-Wide Approach in Addressing Acne With a Multi-Targeting Nutraceutical

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ABSTRACT

Acne vulgaris (AV) is one of the top concerns dermatologists encounter from women. Until now, therapies addressing AV have largely centered around, and have been successful at, targeting the pathophysiological mechanisms that occur at the pilosebaceous unit: sebum hypersecretion, follicular keratinization, over-proliferation of *Cutibacterium acnes*, and a localized immune response. In addition to these, there is good evidence to suggest that other systemic drivers of a generalized inflammatory response may contribute to the development or exacerbation of acne and that addressing these underlying factors may open more opportunities for developing effective treatments. These include psycho-emotional stress, diet and metabolism, hormonal fluctuations, skin and gut microbiome, oxidative stress, and immune response. While there is accumulating evidence that vitamins, minerals, and botanicals may mitigate some of the pro-inflammatory effects from the activation of these underlying systems, their use and recommendations are limited by a lack of quality efficacy and safety evidence. Here, we present the current evidence for the use of individual supplements in addressing the 6 systemic underlying drivers of AV. We also present a clinical study on the safety and efficacy of a nutraceutical combining many of these ingredients in the management of AV in men and women.

J Drugs Dermatol. 2024;23(3):160-167. doi:10.36849/JDD.8138

INTRODUCTION

Acne vulgaris (AV) is the number one skincare concern of women ages 18-50 years and is in the top 3 complaints dermatologists see in their office, with the prevalence increasing across the globe.[1,2] As patients and providers search for effective treatments for such a large portion of the population, the market for treatments is also growing and is expected to increase by 5% compounded annual growth rate by 2030.[1]

In the pursuit of finding effective therapeutics for AV, conventional medicine has characterized the correlation of pathophysiology of the Pilosebaceous Unit (PSU) and AV lesion formation with 4 mechanisms: excess sebum production, follicular keratinization causing an obstructed follicular orifice, and the over-proliferation of *Cutibacterium acnes*, triggering an immune response. With this understanding, options for the management of AV targeting the pathophysiology at the PSU have been developed, from prescription and over-the-counter (OTC) medications to at-home devices.[3,4] Current treatment regimens often include azelaic acid, benzoyl peroxide, or retinoids, which all target follicular keratinization, *C. acnes* proliferation, and inflammation. Oral antibiotics, isotretinoin, hormone therapy, or a combination target all 4 of the underlying mechanisms occurring at the AV lesion site.[5]

While benzoyl peroxide, retinoids, and antibiotics are known to be effective in treating AV, some of these therapeutics are limited in their use as more attention is being paid to the secondary effects associated with their use. For example, dermatologists prescribe antibiotics almost twice as much as providers of other specialties, with strong implications for the rise of antibiotic resistance.[6] Additionally, approximately 37% of acne patients discontinue using acne products because of the side effects.[2]

A growing trend in acne management is for a more integrative, systemic approach, driven by both patients and providers. In addition to the local inflammation at the PSU, there is now a growing body of evidence that suggests that AV may be driven by underlying systemic, immune-inflammatory pathways. Some purported mechanisms include: Psycho-emotional stress leads to a neuroendocrine response and the release of inflammatory cytokines in the skin; Diet and metabolism, such as high glycemic diets, insulin, and aberrant vitamin levels are associated with inflammatory pathways in the skin; Dysbiosis of the gut and skin microbiome can lead to the overgrowth of pathogenic microbes, triggering an immune response; Excess androgens and hormonal fluctuations may stimulate sebocytes and PSU inflammation; Oxidative stress triggered by internal

and external mechanisms causes cellular damage; Finally, dysregulated immune function, oftentimes downstream of the other intertwined systems, is a direct link to the inflammatory response at the PSU. A recent review by Del Rosso et al[71] discusses the current clinical data supporting these as the systemic patient-centric approach to AV.

Natural compounds and dietary supplements, including nutraceuticals used in complementary and alternative medicine, are a growing trend in wellness and beauty and may offer an expanded approach to the treatment and management of AV beyond conventional medicines addressing the pathophysiology only at the PSU.[2,4] For example, vitamin A was one of the first vitamins to be recommended for its role in treating acne and is now the basis for the development of tretinoin and isotretinoin, which are powerful AV treatments.[7] We can also see that treating the systemic drivers of hair thinning has found success, as supplements that provide whole-body support for daily stressors from metabolism, lifestyle, hormones, and others have repeatedly been shown to improve hair thinning over time in different populations.[8-11]

But, while supplements are regulated by the US Food and Drug Administration, they are not subjected to the same standards as drugs, and oftentimes, there is limited data from well-designed clinical studies. Very recently, a systematic review in *JAMA Dermatology* looking for evidence for oral nutraceuticals in the treatment of AV identified 2582 abstracts of which only 42 met their criteria (a total of 3346 participants).[12] Still, the review presented several studies showing encouraging data for the safety and effectiveness of oral nutraceuticals for treating AV and noted vitamin D, green tea extract, probiotics, and several others as having fair- to good-quality studies in this space.[12] Furthermore, fish oil, probiotics, and oral zinc have been studied for their role in treating AV, yet convincing data regarding the safety and efficacy of these agents is still too limited to be recommended in the AAD Guidelines of Care for Management of Acne.[4] Because of this, their use and recommendation for addressing AV is limited.

In this article, we review clinical evidence for various botanicals, vitamins, and minerals to address the systemic root causes of AV (stress, diet and metabolism, hormones, skin and gut microbiome dysbiosis, oxidative stress, and immune response). Although the severity of AV in these studies is not always noted, the type of acne is reported when available. We also present the promising results of a 12-week clinical study using a supplement containing 20 botanicals, vitamins, and minerals supported by evidence to address non-cystic acne or improve skin health. Broadening the scope of therapeutics to include a systemic approach using standardized, effective ingredients could offer a more comprehensive approach to AV management. To continue pushing the field of dermatology forward, we need to bridge the gap between the clinical evidence suggesting systemic drivers of AV and the clinical effectiveness of dietary supplements and botanicals to address those targets. When we do that, we may be able to improve clinical outcomes of AV patients, whether that is used in conjunction with conventional treatments, decreasing the dose or treatment time, or offering more natural solutions for patients who prefer so.

Addressing the Stress Response in the Skin

Clinically, higher reported stress levels have been associated with an increased acne grade in adult women.[13,14] While these data confirm the anecdotal reports of the impact of systemic stress on acne in adult females, there is a lack of therapeutics available to address psycho-emotional stress in the acne patient. Oftentimes suggestions to decrease stress can focus on a lifestyle change, for example, meditation, yoga, and exercise can be recommended to reduce stress that contributes to adult acne.[15]

Alternative medicinal practices have characterized a few botanicals that have been used to manage stress with purported physiological mechanisms. Ashwagandha, a shrub found in Asia and Africa, has now become popular as an "adaptogen," and may prevent the detrimental fluctuations of cortisol and other stress hormones released during a generalized stress response.[16] The natural ayurvedic Holy Basil (*Ocimum tenuiflorum*) has also been used in traditional medicine to combat stress.[17] In a double-blind, placebo-controlled study, adult participants who received Holy Basil showed a significant decrease in the self-reported perceived stress scale as well as a decrease in salivary and hair cortisol levels.[17,18] On a mechanistic level, pre-clinical and clinical studies also indicate additional potential benefits including its antioxidant, analgesic, and anti-inflammatory properties.[19,20] Its medicinal properties are attributed to its biochemically active components such as eugenol, carvacol, and rosmarinic acid.[17] In a recent systematic review, Holy Basil was found to be therapeutically associated with improving psychological, physiological, metabolic, and immunological impacts of lifestyle-related chronic disease.[20] The improvement across these domains is attributed to Holy Basil's anti-inflammatory effects, making it a candidate that may also be useful in targeting the underlying stress-induced inflammation reported in patients with AV.[20]

Diet and Metabolism

Sugar consumption and insulin fluctuation have been directly implicated in the development of AV.[4,21] As such, AV management also includes recommendations for consuming a low glycemic diet and maintaining balanced blood insulin levels. Studies suggest that the anti-diabetic medication metformin that targets gluconeogenesis improves AV in women with PCOS purportedly by reducing hyperinsulinism and the resulting ovarian hyperandrogenism.[22] It has also been suggested that

men with metabolic syndrome or insulin resistance with AV may also benefit from metformin treatment.[23] Beyond this, there are traditional botanicals that have been shown to help with balancing the negative effects of glucose and insulin fluctuations, such as berberine and ginger, which also may improve clinical manifestations of AV.

Berberine (*Berberis aristate*, Indian barberry) is a botanical that has been used in Chinese traditional medicine for hypercholesterolemia, diabetes type 2, and to fight infections.[24] Recent research suggests that it does so in part by improving blood glucose and insulin sensitivity through direct effects on LDL receptors and glucose absorption and uptake.[25-27] Berberine is now being tested for the management of dyslipidemia, diabetes, and obesity.[25-27] In fact, the effects of berberine on plasma lipids are recognized in The European guidelines for the management of dyslipidemias.[28] Now, evidence-based studies have linked potential therapeutically beneficial properties of berberine in AV patients. A 2002 comparative study of a tablet containing berberine vs minocycline in acne patients saw no difference between the 2 groups.[29] Another study in PCOS women with moderate acne reported a 61% decrease in Global Acne Grading System (GAGS) and 71% decrease in Cardiff Acne Disability Index (CADI).[24] Moreover, the relatively minor side effect profile of berberine has seen success when used in patient populations such as those with PCOS or dyslipidemia, where long-term modern therapies were not tolerated.[24] In this sense, berberine could provide a powerful tool against a novel target for patients with AV.

Ginger (*Zingier officinale*), has also been used in traditional medicine for its numerous benefits not only for addressing metabolic disorders, but also for its anti-inflammatory and anti-oxidative properties.[30,31] A meta-analysis examining the benefits of ginger on type II diabetes and the associated hyperglycemia found that HbA1c levels and fasting serum glucose levels improved with the consumption of ginger.[32] On a larger scale, the benefits of ginger were studied in a meta-analysis including patients with type 2 diabetes, non-alcoholic fatty liver disease, and osteoarthritis. They found that the intake of ginger significantly decreased circulating levels of CRP and tumor necrosis factor-alpha (TNF-α).[30]

Another important aspect of the patient's metabolic profile is their consumption of key vitamins and minerals, and as dermatologists, we have been trained to assess this. In patients with AV, low levels of vitamin A, D, and selenium have been reported and there is growing evidence that once corrected, AV may improve.[33-35] Placebo-controlled clinical studies show that supplementing with zinc significantly decreases inflammatory acne scores and improves AV severity in patients.[36,37] Niacinamide (vitamin B3) is a key precursor to the coenzymes NAD/NADP/NADH/NADPH, critical for reduction-oxidation reactions throughout the body.[38] Niacinamide has been shown to have a wide range of purported benefits in the skin: it has antioxidant effects, improves epidermal barrier function, increases dermal collagen and protein production, and reduces hyperpigmentation.[39] Specific to AV, in a formula combined with other ingredients including azelaic acid, zinc, copper, pyridoxine, and folic acid; ingestible niacinamide has been shown to reduce inflammatory papules.[40] Indications suggest that vitamin D may be a potent immune modulator with endocrine, paracrine, and autocrine functions.[38] Finally, women with PCOS who received selenium in a double-blind, placebo-controlled trial had significantly decreased DHEA levels.[41] All of this evidence suggests there may be an overlap of underlying whole-body drivers of AV and a necessity to balance them to manage AV and promote general skin health.

Gut and Skin Microbiome

Antibiotics are a mainstay of acne treatment due to the role of *C. acnes* in the pathogenesis of AV.[42] Both oral and topical antibiotics are commonly prescribed, although short-course therapy is now favored due to the potential for developing antibiotic resistance.[43] Along with this, research suggests that the gut microbiome in patients with AV may be less diverse and has a higher ratio of *Bacteroides* to Firmicutes.[42,44] The gut microbiome has been shown to interact with the nutrient-sensitive kinase mammalian target of rapamycin (mTORC), known to play a role in the pathogenesis of AV.[45] Oral antibiotics also contribute to gut dysbiosis in patients with moderate-to-severe AV.[42,46]

Along the same lines, using milk cultures with bacteria topically to treat AV dates back to the 1930s, showing the use of natural remedies to manage the microbiome and thus the underlying pathogenesis of AV.[47] Current findings now indicate that improved biodiversity of the skin and gut microbiome is essential for epithelial health.[48,49] Clinical studies suggest that supplementing with probiotics may improve symptoms of AV, in part by decreasing sebum production, which could reduce follicular colonization of *C. acnes* and the associated inflammation.[47] It also may have immunomodulatory properties through the inhibition of cytokines in epithelial cells and keratinocytes.[47] Supplementing with commensals has also been suggested to aid in the remediation of leaky gut, leading to an improved inflammatory profile systemically.[50] The daily intake of the heat-killed postbiotic L-137 has been linked to improved skin parameters such as improved TEWL and improved dermatology life quality index in participants with dry skin.[51]

The gut microbes may also interact directly with the intestinal lumen cells by promoting immune responses. Short-chain fatty acids (SCFA) such as butyrate, are synthesized and released in the colon by bacterial fermentation of starches and fibers.[52] Clinical data suggests that patients with AV have an

underrepresentation of *Bifidobacterium* and *Butyricicoccus*, which are primary producers of butyrate.[50] Research suggests that butyrate may play a key role in improving the epithelial defense barrier, improving oxidative status, and relieving mucosal inflammation.[53] It does so in part by providing energy to the gastrointestinal cells.[52] Preclinical research indicates that butyrate may have a pro-apoptotic effect on the cell cycle, as well as effects on proliferation and differentiation.[54] This is believed to be the underlying mechanism in its beneficial effects on hyperproliferative skin diseases such as psoriasis.[54] In addition to directly providing energy and cell cycle control, butyrate may also activate regulatory T cells, which could be a connection to its anti-inflammatory properties.[54]

Hormones

Balancing androgen levels is used to treat AV in the clinic. Combined oral contraceptives mitigate the effect of hormonal fluctuation, improving AV in female patients.[4] Spironolactone is a potassium-sparing diuretic with anti-androgenic properties.[55] It is now used widely to treat female patients with AV and is considered an alternative to antibiotic therapy.[4] Spironolactone is used at doses of 50-100mg/day for treating female patients with mild-to-severe AV but is contraindicated in patients who are pregnant or trying to conceive.[55,56] While efficacious, these treatments are irrelevant to at least half the population or may come with unwanted side effects.[4]

Alternatively, botanicals have been used to mitigate mild effects of excess androgens in conditions such as menopause and PCOS. Maca (*Lepidium meyenii*), for example, is a Peruvian root used in high altitudes to maintain health and energy and address female-specific hormonal imbalances such as infertility and menstrual irregularities.[57] In a double-blind, randomized, placebo-controlled study of early post-menopausal women, the oral intake of Maca tablets was significantly correlated to an increase in E2 production and suppression of FSH and LH.[57] It also was linked to an increase in High Density Lipoprotein (HDL) levels and alleviated the frequency and severity of reported menopausal symptoms such as hot flushes and night sweats.[57] Maca has also been associated with lower serum IL-6 levels and mitigated antidepressant-induced sexual dysfunction.[58,59] All of this suggests that Maca could be a useful botanical supplement for addressing the underlying hormonal component of AV.

Selenium is also now being explored for its role in AV along with its androgen-modulating properties. Selenium levels in patients with AV have been reported as lower than in the general population.[60] In a double-blind placebo-controlled study, women with PCOS who supplemented with selenium for 8 weeks showed significant improvement in AV.[41] The study also noted a decrease in DHEA-S levels, an androgen that has been shown to be elevated in patients with AV.[41] The oral intake of selenium was also associated with a significant decrease in C-reactive protein (CRP) and plasma malondialdehyde (MDA) levels, both markers for oxidative stress.[41] When taking a patient-centric view, these findings suggest a link between decreased inflammation, oxidative stress, and AV improvement.

Oxidative Stress

While oxidative stress has not been specifically targeted by modern medicine in the clinic, many of the natural anti-aging phytochemicals with purported benefits in the skin in use today contain anti-oxidative properties. Lycopene, for example, in high concentrations in tomatoes, has been shown to inhibit oxidative markers that are generated in the skin during exposure to ultraviolet (UV) A and UVB.[61] The oral intake of olive oil, long used for its supposed beneficial effects on the skin, was linked to a dose-dependent increase in HDL and the intracellular antioxidant glutathione peroxidase (GSH-Px), and a dose-dependent decrease in plasma oxidized LDL and other oxidized DNA and poly-unsaturated fatty acid (PUFA) markers.[62] It was also associated with an increase in plasma concentrations of antioxidants such as tyrosol, hydroxytyrosol, and 3-O-methylhydroxytyrosol (MHT), a biological metabolite of hydroxytyrosol.[62] In addition, a systematic review and meta-analysis concluded that ginger supplementation significantly reduced MDA levels as well as GSH-Px, both markers for oxidative stress.[31]

Sicilian orange, also known as blood oranges or Red Orange (*Citrus sinensis*, varieties *Moro, Tarocco, and Sanguinello*) has demonstrated high levels of antioxidative properties. A significant crop grown and exported in high-UV regions such as Italy and Egypt, blood oranges and their peels are rich sources of vitamin C.[63,64] Their consumption for anti-aging properties is now being explored. An extract of these Sicilian Red Oranges has been shown to contain high levels of antioxidants such as anthocyanins, hydroxycinnamic acids, flavanones, and ascorbic acid.[63] A recent study showed that consumption of this complex decreased UV-induced skin redness, in part by increasing the total antioxidant capacity of the skin.[63] MDA levels were significantly lower in the active group, indicating a decrease in lipoperoxide levels due to UV stimulation.[63] With the strong indications for UV damage and its role in AV development and epidermal integrity, antioxidants may be useful in the mitigation of this damage, which could improve skin health.

Immune Function

Considering that the systemic drivers discussed here and in Del Rosso et al[71] have been linked to pathways that may drive generalized immuno-inflammatory activation, targeting and attenuating components of an irregular immune system could improve AV outcomes. Curcumin, the golden component of turmeric, is widely known for its use in Asian and Indian cuisine. It has also been used for centuries for its anti-inflammatory properties and is now being investigated for its

use in inflammatory bowel disease, colon cancer, psoriasis, rheumatoid arthritis, and a multitude of other inflammatory conditions.[65,66] New insights into molecular pathophysiology now indicate that curcumin may attenuate the generalized inflammatory response in part by lowering circulating levels of TNF-α and CRP, key inflammatory mediators released during injury or tissue damage.[65] In fact, TNF-α inhibitors used to treat other inflammatory diseases are sometimes used off-label to treat cases of severe AV that are not responsive to other treatments.[67] Curcumin may also prevent the onset and development of an inflammatory response by suppressing the transcription factor NF-kB, a key regulator of genes associated with generalized inflammation.[68]

Indirectly, curcumin mitigates a generalized inflammatory response through its protective effects as an antioxidant. Curcumin's polyphenolic structure acts as a free radical scavenger, which could improve antioxidant capacity in the skin to mitigate damage by UV and environmental assaults.[68] It has also been shown to increase the cellular antioxidant GSH, which would prevent ROS-induced tissue damage.[68] Studies specifically in fibroblasts and keratinocytes have shown increased protective effects of curcumin against H2O2.[68]

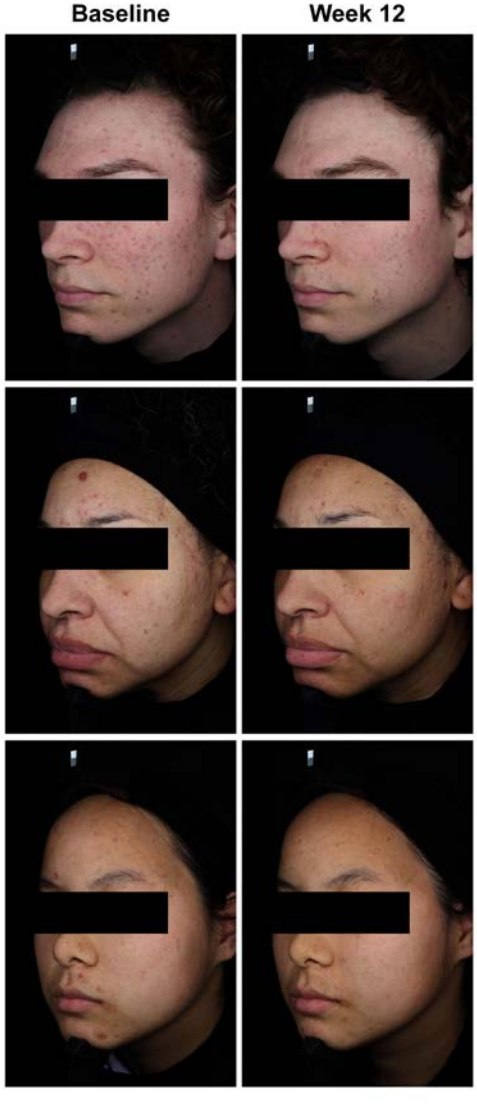
Important in AV, curcumin has also been shown to have anti-microbial properties against opportunistic microbes such as *S. epidermis* and *C. acnes*. With this, curcumin has been linked to the suppression of bacterial proliferation and the formation of biofilms by decreasing adhesion molecules of the microbes.[68] Knowing that antibiotics have proven successful in the treatment of AV, these antimicrobial properties could also be a tool to improve outcomes in patients with AV.

Considering curcumin's compelling therapeutic profile, much focus has been on improving its limited bioavailability in its natural form. Patented biotechnology has found that reconstituting 95% standardized curcumin in non-curcuminoid oil from turmeric improves bioavailability by almost 700% compared to curcumin alone.[69] With this, the therapeutic potential of curcumin described for centuries can be incorporated into dietary intake.

Clinical Support for the Combination of a Standardized Acne Supplement

As reviewed here, several ingredients have been clinically studied to improve some of the underlying root causes of acne on their own. One would expect, then, that combining varying amounts of key ingredients could theoretically have better clinical results compared to single target ingredients that have thus been evaluated in patients with acne. A novel nutraceutical was recently formulated to include key ingredients to address multiple systems-wide root causes of acne (Table 1). This combination nutraceutical could potentially enable less usage of any one specific ingredient and have the benefit of the multi-faceted approach.

FIGURE 1. Cross polarized images of baseline and week 12 timepoints in 3 participants with mild-to-moderate acne.



The Standardized Nutraceutical was evaluated in a proof-of-concept study conducted in 51 adults with non-cystic acne. The study was approved by an Institutional Review Board (Advarra IRB, Columbia, MD) and conducted in accordance with accepted standards for Good Clinical Practices. All participants provided written informed consent prior to participating, consistent with the requirements in 21 Code of Federal Regulations (CFR) 50.25. This was a 12-week single-arm prospective study for women and men aged 18 to 50 years with facial acne ranging from mild to severe, excluding cystic acne. Participants discontinued all acne medications and topicals prior to the start

TABLE 1.

Selection of Key Ingredients in a Standardized Nutraceutical for Skin		
Synergen Skin Complex	**Additional Key Ingredients**	**Nutrient Supportive Ingredients**
Holy Basil	Olive Extract	Vitamin A
Maca	Konjac Root	Vitamin B3 (Niacinamide), B5 (Pantothenic Acid), B9 (Folate)
Curcumin	Tributyrin	Vitamin C
Berberine	Probiotic (B. subtilis DE111®)	Vitamin D3
Postbiotic (HK *L. Plantarum*)	Lycopene	Selenium
Sicilian Orange	Ginger Extract	Zinc

TABLE 2.

Improvements in Acne and Skin Parameters				
Measurement	**Baseline**	**Week 12**	**% of Subjects Improved**	***P* value**
IGA of Acne Severity	2.5	1.7	85	<0.001*
Lesion Count				
Inflammatory	8.0	5.2	69	<0.001*
Non-inflammatory	19.4	10.3	87	<0.001*
Bioinstrumentation				
Sebumeter	158.1	121.6	72	0.002+
Corneometer	35.0	42.8	74	0.002+
Tewameter	18.6	19.9	41	0.361+

Mean values reported. *Determined through Wilcoxon-signed rank test. +Determined through paired t-test. Significance set at *P* values <0.05

of the study. Clinical assessments at baseline and weeks 4, 8, and 12 included Investigator Global Assessment (IGA) of acne severity, inflammatory and non-inflammatory lesion counts, and clinical grading of skin health, including post-inflammatory hyperpigmentation/erythema (PIH/PIE). Bioinstrumentation (corneometer, tewameter, sebumeter) and subjective questionnaires on perception of efficacy were also completed at each visit.

Significant and progressive improvements were seen in acne parameters, shown in Table 2. Specifically, IGA of acne severity showed a decrease of 30% from baseline to week 12 (baseline: 2.47 ± 0.60, week 12: 1.73 ± 0.71) . In addition, IGA scores of acne severity improved in 85% of the participants by week 12. Average lesion counts also significantly decreased throughout the study, with a 35% decrease in inflammatory lesion counts and 47% decrease in non-inflammatory lesion counts (Table 2). Overall, clinical grading of skin quality parameters progressively and significantly improved throughout the study. Notably, post-inflammatory hyperpigmentation/ post-inflammatory erythema (PIH/PIE) parameters improved in nearly 80% of participants by week 12. Skin hydration as measured by the corneometer also improved in 74% of subjects. Sebumeter measurements improved significantly with a decrease of 25% as early as week 4 and remained lower than baseline throughout the study. Participants also reported improvements at 12 weeks, including "clearer skin," "less breakouts," "less oily skin," and that their "acne had improved" (87%). Although preliminary, these results are promising and warrant further research. A randomized, placebo-controlled trial is currently underway.

CONCLUSION

Conventional treatments, while shown to be clinically effective in decreasing the severity of AV, are becoming more challenging to access with insurance companies often denying prescription medications for AV. In addition, side effects, including antibiotic resistance, photosensitivity, and pregnancy contraindications, are of concern to many patients considering oral therapies for AV. These barriers to treatment are a significant challenge for AV patients, leading many to search for alternatives that are safe and effective. Additionally, therapeutic options that reduce the need for topical and/or oral antibiotic therapy for AV are an important focus, as bacterial resistance to antibiotics is a clinically relevant concern both in the United States and globally.

Dermatologists are also recommending an increasing number of OTC treatment options as they are more easily accessible and affordable for patients. While effective, OTC treatments still target the conventional, local AV pathophysiology described as 4 major pillars at the site of the acne lesion. There is, however,

substantial support that whole-body factors such as stress, diet and nutrition, gut and skin microbiome, hormones, oxidative stress, and immune function contribute to a generalized, dysregulated immune-inflammatory response. This was discussed in a recent review from Del Rosso et al.[71] Now, the authors propose the consideration of therapeutics that have traditionally been used, and have clinical support, to address these systemic dysregulations on a patient-centric level.

Complementary and alternative medicine (CAM), such as nutraceuticals, have long been explored for their use in improving skin health, but the paucity of scientific evidence and lack of clinical data on the safety and efficacy have limited their recommendation for use in the clinic for AV. Now, scientific literature is bridging the gap with clinical evidence that provides support for a systemic, multi-targeting approach. The approach does not reject the established, effective therapeutics that are available to us, rather it proposes an expanded consideration using evidence-based studies to provide a more comprehensive approach to AV management. In this paper, we provided the current evidence suggesting that many botanicals, vitamins, and minerals may be available to address underlying drivers of AV that conventional medicines ignore.

When combined, these ingredients may have the potential to improve AV and skin health. A 12-week proof-of-concept study showed improvements in AV and skin parameters in adults with mild-to-severe AV. Although more studies are needed, these results offer insight into the potential benefits of nutraceuticals addressing underlying mechanisms that up to now, have gone largely unexplored. Addressing dysregulation that contributes to a generalized inflammatory response in a patient-centric manner may prove to be an important step in expanding our toolbox in providing more options for AV management and improving skin health.

DISCLOSURES

Dr Burgess is a clinical investigator for Nutraceutical Wellness LLC but has not received compensation or services for any aspect of the submitted work. Dr Gold is a consultant for Nutraceutical Wellness LLC and is paid for those services. Dr Farris is a paid advisor for Nutraceutical Wellness LLC. Dr Hazan and Dr Raymond are employees of Nutraceutical Wellness LLC.

ACKNOWLEDGMENT

The authors would like to acknowledge the contributions of Nicole Townsend and Ryan McLendon for their research assistance.

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doi:10.36849/JDD.7697

March 2024 168 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Survey of the Prices of Topical Compounded Medications for Alopecia in the Tri-State Area

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ABSTRACT

Background: Currently, there is only one topical medication approved by the US Food and Drug Administration for alopecia, minoxidil 2.5% and 5%. With limited options, dermatologists often turn to compounding pharmacies for customized topical alopecia medications.
Objectives: (1) to investigate the pricing and availabilities of compounded topical alopecia medications and (2) to investigate the delivery/mail options available.
Methods: 103 dermatological compounding pharmacies in the tri-state area were contacted. Data were collected on the prices of 11 different compounded formulations for alopecia, the highest concentration of minoxidil available, compounding accreditation status, and delivery.
Results: The majority (76.7% [79/103]) of pharmacies surveyed were responsive. Mean prices for 60 g or mL of medication were $70.44 for minoxidil 5%, $86.95 for minoxidil 5%/finasteride 0.5%, $159.13 for minoxidil 5%/bimatoprost 0.03%, $141.91 for minoxidil 5%/latanoprost 0.02%, $75.31 for finasteride 0.5%, $204.41 for tacrolimus 0.3%, $220.11 for tacrolimus 0.3%/minoxidil 5%/clobetasol 0.05%, $71.44 for cetirizine 1%, $74.93 for metformin 10%, $4,273.20 for tofacitinib 2%, and $1,840.42 for ruxolitinib 2%.
Nearly all (93.5% [72/77]) of the pharmacies reported being able to compound minoxidil higher than the commercially available 5%, while 67.6% (50/74) were able to customize minoxidil to be made with <10% alcohol.
Just over half (56.4% [44/78]) of the pharmacies were able to deliver to all tri-state areas. The mean delivery fee of pharmacies was $5.93 (n=77). Almost all of the pharmacies (98.7% [76/77]) claimed to be able to process and deliver medications within a week. If pharmacies were not located in the local vicinity, 44.6% (29/65) used a mailing service.
Conclusion: This survey serves to expand clinicians' and patients' knowledge of the options and prices of topical compounded medications for alopecia.

J Drugs Dermatol. 2024;23(3):168-172. doi:10.36849/JDD.7697

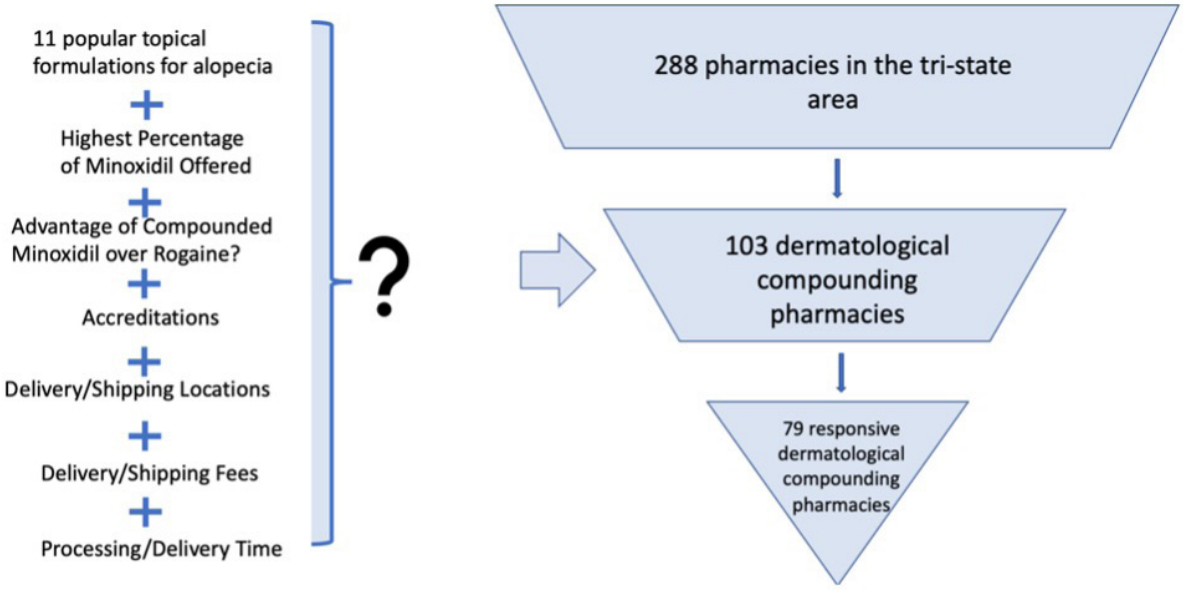
INTRODUCTION

Compounding pharmacies are pharmacies that can prepare unique formulations of topical medications, modify existing formulations of drugs, and create a variety of off-label formulations specific to a patient's needs. These pharmacies can be particularly useful to dermatologists as different topical active ingredients can be prepared outside of what is commercially available. Alopecia is one condition for which dermatologists commonly rely on compounding pharmacies. Currently, only one topical medication, minoxidil (2.5% and 5%), is approved by the United States Food and Drug Administration (FDA) for the treatment of alopecia.[1] This medication is currently only available commercially in foam and solution form.

According to the American Pharmacists Association, there are over 7,500 pharmacies in the U.S.. that specialize in compounding services. Treatments for alopecia are often not covered by insurance, and the out-of-pocket costs of these medications are highly dependent on the pharmacy itself. As information on the prices and formulations of these compounds is not readily available, a survey was created to address this lack of knowledge.

This study aims to investigate the pricing and availabilities of compounded topical alopecia medications and to investigate the delivery and mailing options available.

FIGURE 1. Methods for survey.



MATERIALS AND METHODS

We contacted by telephone 291 pharmacies identified online as compounding pharmacies in the tri-state area (New York, New Jersey, Connecticut). The surveys were conducted from June 2022 to August 2022. Responses were included if the pharmacy confirmed that they compound, and if they responded to at least 1 question. Data were collected on the prices of 11 different compounded formulations for alopecia (for 60 g or 60 mL): minoxidil 5%, minoxidil 5%/finasteride 0.5%, minoxidil 5%/bimatoprost 0.03%, minoxidil 5%/latanoprost 0.02%, finasteride 0.5%, tacrolimus 0.3%, tacrolimus 0.3%/minoxidil 5%/clobetasol 0.05%, cetirizine 1%, metformin 10%, tofacitinib 2%, and ruxolitinib 2%. These medications were chosen by the authors to represent a variety of popular treatments for various types of alopecia.

Responses were elicited for the highest percentage of minoxidil compounded, compounding accreditation status, processing and delivery times, and the pharmacists' perspectives on the advantages of specific compounded formulations over commercially available options (Figure 1). If the pharmacies were able to compound the two JAK inhibitors, tofacitinib and ruxolitinib, they were also asked if they were able to compound the JAK inhibitors using a liposomal base.

Responses were excluded for pharmacies that did not give prices without a prescription, were unresponsive, or gave the prices for a quantity other than the amount specified (60 g or 60 mL). Descriptive statistics were performed. Pearson correlation coefficients were found for the prices of minoxidil 5% compared to the prices of the other medications.

RESULTS

Of the 291 pharmacies that were surveyed, 103 were identified as pharmacies that compound topical dermatological medications with a response rate of 76.7% (79/103).

Average prices for the compounding medications were calculated (Table 1). The smallest range in price for medication was $90.00 for cetirizine 1% and the largest range was $14,935.00 for tofacitinib 2%.

Of the pharmacies that were able to compound tofacitinib 2%, 90.9% (20/22) were able to compound it using a liposomal base. And, 83.3% (5/6) of the pharmacies that were able to compound ruxolitinib 2% were able to compound it using a liposomal base.

Minoxidil, commercially available at 2.5% and 5%, can be compounded at higher percentages. The highest concentration of minoxidil ranged from 5% to 15% with 10% minoxidil being the most popular response (Table 2). Most of the pharmacies (93.5%) reported being able to compound minoxidil at a concentration higher than the commercially available 5%. About two-thirds of the pharmacies (67.6%% [50/74]) reported that they were able to compound minoxidil using a base with <10% alcohol. The mean cost of 5% minoxidil using a base with less than 10% alcohol was $74.38, which is only $3.94 more than the mean cost of 5% minoxidil with any percentage of alcohol in this study.

Pearson's correlation coefficients were found for the prices of minoxidil 5% compared to the prices of the other medications to determine if the price of minoxidil could be used as a predictor

TABLE 1.

Average Prices of Selected Compounded Topical Medications

Medication (concentration)	Mean price in dollars	Median price in dollars	Range (minimum price, maximum price) in dollars	Response Rate (%)	Pharmacies unable to compound this medication (%)
Minoxidil 5%	70.44	70.22	104.00 (16.00, 120.00)	65.0	9.7
Minoxidil 5%/Finasteride 0.5%	86.95	85.00	146.00 (45.00, 191.00)	63.1	10.7
Minoxidil 5%/ Bimatoprost 0.03%	159.13	140.00	325.00 (55.00, 380.00)	35.0	36.9
Minoxidil 5%/Latanoprost 0.02%	141.91	100.00	335,00 (45.00, 380.00)	29.1	39.8
Finasteride 0.5%	75.31	75.00	140.00 (30.00, 170.00)	62.1	8.7
Tacrolimus 0.3%	204.41	150.00	645.05 (54.95, 700.00)	55.3	14.6
Tacrolimus 0.3%/ Minoxidil 5%/ Clobetasol 0.05%	220.11	177.50	615.00 (60.00, 675.00)	51.4	15.5
Cetirizine 1%	71.44	68.75	90.00 (35.00, 125.00)	34.0	33.0
Metformin 10%	74.93	70.00	142.00 (30.00, 172.00)	62.1	9.7
Tofacitinib 2%	4273.20	5000.00	14,935.00 (65.00, 15,000)	21.4	53.4
Ruxolitinib 2%	1840.42	2000.00	3,152.50 (147.50, 3300.00)	5.8	67.0

TABLE 2.

Highest Concentration of Minoxidil Available and Mean Prices

Highest percent of minoxidil offered	Percentage (out of 75 responses)	Mean price for 60 g or 60 mL in dollars
5%	6.7%	86.00
6%	1.3%	87.50
7%	10.6%	63.73
7.5%	1.3%	60.00
8%	5.3%	81.67
9%	1.3%	135.00
10%	48.0%	84.00
12%	5.3%	93.75
15%	20.0%	98.98

for the affordability of other topical alopecia medications (Table 3). The medications that positively correlated with the price of minoxidil 5% were minoxidil 5%/finasteride 0.5%, finasteride 0.5%, cetirizine 1%, and metformin 10%.

Among the 79 compounding pharmacies, only 20 pharmacies had compounding accreditations. Of those, 13 pharmacies specifically had the Pharmacy Compounding Accreditation Board (PCAB) certification. Other accreditations included the National Association of Boards of Pharmacy (NABP) (4), Utilization Review Accreditation Commission URAC (2), and the Board of Certification BOC (1). We also found that 20 pharmacies were members of a compounding organization/network and 4 were in the process of obtaining PCAB. Thirty-eight pharmacies did not have any accreditations or memberships with compounding organizations. PCAB accreditation was not significantly associated with lower prices of minoxidil (P=0.33) or minoxidil 5%/finasteride 0.5% (P=0.59).

Pharmacists were asked about the advantages of compounded minoxidil over commercially available OTC minoxidil. The 4 most popular responses were (1) the ability to customize concentration (23 responses), (2) no difference and they would be unable to compound medications with identical concentrations of commercially available products (14 responses), (3) the ability to compound medications with a combination of different ingredients to make the product more effective (13 responses), and (4) the ability to compound different forms of medications such as foam, gel, solution, etc. (4 responses).

More than half (56.4% [44/78]) of pharmacies were able to deliver to all tri-state areas, but the rest were limited to their state or county. The mean delivery fee of pharmacies was $5.93 (n=77) and nearly half (42.6%) of the pharmacies had a $0 delivery fee. Additionally, all but 1 pharmacy claimed to be able to process and deliver medications within a week, while 53.2% of pharmacies claimed to be able to process and deliver the medication within 4 days. If the pharmacies surveyed were not in the local vicinity of the patient, 44.6% (29/65) of pharmacies

TABLE 3.

Correlations Between Minoxidil and Other Topical Medications

	Minoxidil 5%/ Finasteride 0.5%	Minoxidil 5%/ Bimatoprost 0.03%	Minoxidil 5%/Latanoprost 0.02%	Finasteride 0.5%	Tacrolimus 0.3%	Tacrolimus 0.3%/ Minoxidil 5%/ Clobetasol 0.05%	Cetirizine 1% Price	Metformin 10% price
Minoxidil 5%	0.56 (P<0.001)	0.43 (P=0.01)	0.10 (P=0.6)	0.55 (P<0.001)	0.31 (P=0.03)	0.34 (P=0.02)	0.67 (P<0.001)	0.65 (P<0.001)

said they would be able to use a mailing service (eg, USPS, UPS, FedEx) to mail medications. If the pharmacies were located near the patient, 55.4% (36/65) of pharmacies reported being able to use their own courier service to deliver locally.

DISCUSSION

Prices

The prices of each medication varied widely among the pharmacies with the lowest range being a $90.00 difference. This indicates the prices for these medications are not similar within pharmacies.

The cost of minoxidil could be used as a predictor for 4 medications (minoxidil 5%/finasteride 0.5%, finasteride 0.5%, cetirizine 1%, and metformin 10%). This suggests that finding out the affordability of minoxidil 5% from one pharmacy can be used as a strategy to predict the affordability of some of the other topical alopecia medications at that pharmacy.

Accreditations

To be able to both compound medications and mail medications to a particular state, compounding pharmacies must be certified by their respective state board of pharmacy. Unlike state board certifications, accreditations are not mandated for compounding pharmacies. Instead, voluntary accreditation programs require additional standards to the ones required by the state and federal governments.

PCAB accreditation was the most popular accreditation of the surveyed pharmacies. PCAB is a service used by the Accreditation Commission for Health Care (ACHC) and functions as a third-party accreditation organization. PCAB accreditation is given to pharmacies that can perform sterile compounding while meeting the PCAB/ACHC quality standards and quality control. Additionally, they must submit for regular inspection by the ACHC. While this accreditation is not necessary for pharmacies to be able to compound nonsterile preparations, having this accreditation ensures that the medications follow the standards for not only the nonsterile compounding process for topical medications defined by the United States Pharmacopeia (USP) <795>, but also additional PCAB-specific quality standards, training, and on-site specific inspections.

PCAB accreditation was found to not be significantly associated with price. However, accreditations may still be something for clinicians to consider when selecting a pharmacy as they have stricter guidelines to follow for quality control.

Advantages of Compounding Medications

Based on the pharmacists' responses, the primary advantage of compounded medications is the ability to manipulate the concentrations of the active ingredients. For instance, with minoxidil, compounding pharmacies can compound as high as minoxidil 10%, which is comparatively higher than the commercially available 2.5% and 5%. A study examining female patients with androgenetic alopecia who failed to respond to minoxidil 5% found that a higher concentration of minoxidil of 10% was effective with no significant adverse events seen at the higher concentration.[2] Compounded minoxidil provides patients who have been unresponsive to minoxidil 5% an additional option.

Additionally, compounding allows for the modification of inactive ingredients. Commercial minoxidil can cause contact and allergic dermatitis as some ingredients like propylene glycol are known allergens.[3] Alcoholic solutions like commercial minoxidil are known to be drying and irritating to the scalp in some patients.[4,5] Minoxidil topical foam/solution can be made from a base that has higher absorptive properties and with less irritating, inactive ingredients. The survey found that minoxidil 5% compounded with a base of less than 10% alcohol was only $3.94 more expensive than the traditionally compounded 5% minoxidil. Thus, compounding is a viable option for patients with specific allergies.

Compounding pharmacies also offer the option to mix multiple ingredients together for combination therapy, such as minoxidil and finasteride. The ability of compounding pharmacists to combine multiple active ingredients, as well as to compound into different forms, such as foam, allows for easier application of the topical medication by the patient.

Limitations of Compounding Medications

The major limitation of utilizing compounding pharmacies is that compounded medications are not FDA-approved. The FDA designated "503B" compounding pharmacies as those that use outsourcing facilities to manufacture large batches of medications for office and hospital use only and require adherence to the Current Good Manufacturing Practice (CGMP) regulations, which were created by the FDA. On the contrary, "503A" compounding pharmacies are those that make medication on demand for patients, are regulated on a state-by-state basis, and are exempt from the CGMP regulations.

Of note, although compounding pharmacies are not FDA-regulated, they are regulated by the state as an exemption to the Federal Food, Drug, and Cosmetic Act of 1938. State boards of pharmacies may utilize regulations defined by the USP Convention for non-sterile USP <795> compounds, which control the allowed variance of the active ingredient, quality assurance, and quality control.[6] In the tri-state area, USP <795> compliance is required for non-sterile, topical medications. For sterile and injectable medications, there are additional requirements that compounding pharmacies must follow.

There are risks involved in compounding medications that are not FDA-approved for safety, effectiveness, and quality. Firstly, serious patient illness and death have been linked to

poorly compounded drugs, most infamously being the fungal meningitis outbreak in 2012, which led to 62 deaths. Although this incident led to the placement of outsourcing compounding companies, which manufacture compounds in bulk to sell to pharmaceutical companies under FDA jurisdiction, traditional compounding companies remain under state regulation.

Secondly, there are no standard labeling regulations for compounding pharmacies, and as such there is a risk of adverse drug events (ADEs) due to lack of instructions or warning of risks and side effects. Compounding pharmacies are not mandated to report adverse drug events to the FDA, and incidences of ADEs are hard to track, as incidences are only noted voluntarily and through mass media.[7] When prescribing compound medications, providers should have an open discussion with their patients about the implications and reasons for prescribing a drug that is not FDA-approved.

Processing and Delivery/Shipping

Pharmacies play a pivotal role in the medical community, providing access to therapeutics and assisting in the management of disease. As such, pharmacy accessibility is critical for healthcare. Notable barriers to pharmacy access include transportation, hours of operation, and expense. Home delivery is one method to reduce these barriers, promoting increased medication compliance[8] and helping to reduce healthcare disparities by providing wider access to patients.

The majority of compounding pharmacies offered delivery services at a free or relatively low cost and nearly half were able to ship to any location in the tri-state area. To be able to ship to another state, the pharmacy must be registered with that state board of pharmacy as well, which accounts for the lower-than-ideal percentage of pharmacies that can ship out-of-state. Nonetheless, the ability of some compounding pharmacies to deliver out-of-state increases medication access for patients.

All pharmacies promised processing and delivery times under 1 week, and over half of the pharmacies claimed to take under 4 days. A problem that has been cited with the use of compounding pharmacies is delay in drug delivery causing missed doses of medication.[9] Thus, it is important for providers to be aware of processing and delivery times when utilizing compounding pharmacies.

Limitations of the Study

One limitation of this study is that prices are often subject to fluctuations, so the prices listed here may not accurately reflect the future market price. Similarly, the availabilities of the medications differ weekly, and if the pharmacists do not have the ingredients at hand, there can be additional time (usually 1-2 business days) required to order and receive the necessary ingredients. Additionally, the study was restricted to pharmacies in the tri-state area. In reality, patients have a much wider range of compounding pharmacies available to them. Because many compounding pharmacies can ship out-of-state, patients living in the tri-state area can use pharmacies from states like Florida or California, albeit with longer delivery times. Also, the prices for each of the medications were not specified based on the forms available, but on the least expensive option. Some forms, such as foam, require additional prep and are more costly than gel or solution forms. Yet, some pharmacies only offer one form, and thus the same medication may seem particularly costly or inexpensive at a different pharmacy.

Another limitation of this current study is that pharmacies were not asked whether they were 503A or 503B regulated. 503B-regulated pharmacies are subject to stricter CGMP guidelines by the FDA, may have limited variability of compounded options, but can potentially have relatively lower costs and are safer. For example, SKNV is a 503B facility that provides minoxidil 7%-finasteride 0.1% solution for a flat fee of $49/60 mL per glass bottle and free shipping.

CONCLUSION

In conclusion, the mean prices and ranges of the compounding medications show great variability in compounding medication pricing in the tri-state area. Compounding medications give patients more options for those who find the commercially available medications ineffective or irritating. However, one must be aware that compounded medications have not been FDA-approved. This survey serves to expand providers' and patients' knowledge of the options and prices of topical compounded medications for alopecia.

DISCLOSURES

The authors have no conflicts of interest to disclose, financial, or otherwise.

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doi:10.36849/JDD.7243e

March 2024 173 Volume 23 • Issue 3

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Beyond Wrinkles: A Comprehensive Review of the Uses of Botulinum Toxin

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ABSTRACT

Background: Botulinum neurotoxin (BoNT) exhibits inhibitory effects on the neuromuscular junction, and its use is well established in cosmetic dermatology. Our review aims to analyze the evidence for its use in the treatment of various dermatological, neurological, gastroenterological, ophthalmological, otorhinolaryngological, dental, urological, gynecological, and cardiovascular disorders.

Methods: A systematic review of the literature was performed for studies published between 2012 and 2022 that discussed the therapeutic use of BoNT in human participants. A total of 58 studies were selected for inclusion in this review.

Results: We discovered a large range of therapeutic applications of BoNT toxin beyond aesthetic and US Food and Drug Administration (FDA)-approved non-aesthetic uses.

Conclusions: BoNT is a powerful neurotoxin that has varied FDA-approved indications and has been studied in a wide range of therapeutic applications. Further investigation through higher power studies is needed to assess the potential of BoNT and expand its versatility across other medical specialties.

J Drugs Dermatol. 2024;23(3):173-186. doi:10.36849/JDD.7243e

INTRODUCTION

Botulinum neurotoxin (BoNT) is the most potent neurotoxin in existence.[1] BoNT is derived from *Clostridium botulinum*, a gram positive, anaerobic, spore-forming bacteria.[2] *C. botulinum* produces many subtypes of toxin, denoted A through G. However, only subtypes A, B, E, and F have demonstrated effects in humans.[2,3] Botulinum toxin cleaves SNARE proteins responsible for the presynaptic release of acetylcholine.[4] Inhibition of acetylcholine release prevents depolarization of the postsynaptic muscle fiber and subsequent skeletal muscle contraction.[3] This produces a classical flaccid paralysis. This effect is harnessed clinically in the treatment of a variety of conditions. Botulinum toxin subtypes A and B are the only subtypes currently used in clinical formulations.[2]

The first known clinical use of BoNT was for the treatment of strabismus. Dr Alan B. Scott, an ophthalmologist, first published his use of an intramuscular injection of an A-toxin containing formulation in 1980.[5] He named his formulation Oculinum, and later sold it to Allergan.[2] The first FDA-approved botulinum toxin formulation, Allergan's Botox, was approved in 1989 for strabismus, blepharospasm, and hemifacial spasm.[3] In 2002, Botox was approved for its renowned use in the treatment of glabellar rhytides.[2] Botulinum toxin is now available in a variety of formulations and has been approved for a variety of indications.

Different formulations of BoNT are available. Those FDA-approved and currently on the market in the United States include Botox (*onabotulinumtoxin A*), Xeomin (*incobotulinumtoxin A*), Dysport (*abobotulinumtoxin A*), and Myobloc (*rimabotulinumtoxin B*). Botox is indicated for cosmetic treatment of rhytides of the glabella, lateral canthus, and forehead.[6] Xeomin is indicated for cosmetic treatment of rhytides of the glabella in adults.[7] Dysport is indicated for cosmetic treatment of rhytides of the glabella in patients less than 65 years old.[8] Myobloc is not indicated for cosmetic use and its on-label FDA-approved uses will be described later in this paper.[9]

These formulations differ in their toxin concentration, which directly impacts the units administered for treatment. Most formulations, other than Myobloc, require reconstitution with saline. Xeomin notably does not require refrigeration. The different formulations also demonstrate variable durations of effect. For example, Dysport has been noted to have a longer duration of action than Botox, possibly due to higher toxin concentrations.[3]

Xeomin contains the least human serum albumin (HSA) content of the available formulations.[3] HSA is used as an excipient stabilizer in all commercially available preparations. This is

doi:10.36849/JDD.7243e

relevant when considering the immunogenicity of BoNT and the rarely noted phenomena of neutralizing antibody formation and resistance to BoNT. Neutralizing antibodies formed against BoNT may be triggered by HSA.[3] These may occur in cases of repeated, high dose, or long term injections.[10] This makes Xeomin an appealing option if there is concern for treatment failure due to antibody formation and toxin neutralization. However, no data exist to support the clinical effect of lower HSA content.[3]

Another reason that toxins can be clinically ineffective is immune resistance. Like the formation of neutralizing antibodies, this phenomenon can similarly occur after higher dose administration, which also predisposes the patient to dose-dependent adverse effects.[10] When suspecting apparent resistance to BoNT, administration techniques must always be reviewed as this effect, or lack thereof, could also be due to insufficient quantity or errors in technique of injection.[10]

A new formulation, *prabotulinumtoxin A* (Jeuveau/Neuronox/Nabota) was approved by the FDA in 2019.[3] *DaxibotulinumtoxinA* (DAXI), which contains no HSA, is also currently under review by the FDA. Both formulations are approved for treatment of glabellar rhytides.[11] Several other formulations are under development or available in other countries, but are not yet approved by the FDA or available in the United States.

The targeted muscles for treatment of rhytides are the procerus, corrugator, frontalis, and orbicularis oculi muscles.[6] Other off-label aesthetic uses of BoNT include treatment of the "gummy smile" by targeting the levator labii superioris alaeque nasi, levator labii superioris, zygomaticus major, and depressor septi nasi muscles; "downturned smile" by targeting the depressor anguli oris muscles; and "cobblestone chin" by targeting the mentalis.[2,12] BoNT may also be employed to treat horizontal lines, vertical lines, and platysmal bands of the neck.[2] Eyebrow lift, nasal bridge lines, perioral rhytides, and "marionette" lines are other off-label uses of BoNT in cosmesis.[13] Finally, aesthetically displeasing muscle hypertrophy in the masseter and gastrocnemius has been addressed with BoNT.[2] Masseter hypertrophy has been associated with bruxism, which will be discussed later in this paper.

Beyond these aesthetic uses, the literature reveals use of BoNT in a variety of other conditions. This paper serves to review the medical uses of BoNT published in the literature.

MATERIALS AND METHODS

A review of the literature was performed using PubMed. An initial literature search with the search phrases "medical uses of botulinum toxin", and "noncosmetic uses of botulinum toxin" was conducted in June 2022 filtering for publications from 2012 to 2022, which yielded a total of 64 results. Exclusion criteria included case reports, articles written in a non-English language, articles without full text available, and articles studying non-human subjects. Only studies published within the last 10 years (2012-2022), written in English language, available in full text, and studying human participants were included.

Of the initial search, 2 articles were duplicates. We excluded 31 papers based on the title and abstract, 1 paper with no full text available, and 1 paper written in a non-English language (Chinese). Twenty-seven articles from the initial searches were further reviewed as follows:

Dermatology: Five articles from the original 27 articles were selected based on review of the title and abstract for relevance. Citations were reviewed and 3 additional articles were selected. A total of 8 articles were included.

Neurology: Fourteen articles from the original 27 articles were selected based on review of the title and abstract for relevance. Citations were reviewed and 4 additional articles were selected. Two papers outside of the original search were also included. A total of 20 articles were included.

Gastroenterology: Two articles from the original 27 articles were selected based on review of the title and abstract for relevance. Citations were reviewed and 2 additional articles were selected. Additional PubMed searches, including search phrases "botox + achalasia" and "botulinum toxin + anal fissures," were performed with filters for articles published between 2012 and 2022 and "abstract," "free full text," and "full text available" with a total of 49 results. Forty-six were excluded based on title and abstract and 3 articles were selected for inclusion. A total of 7 articles were included.

Otorhinolaryngology: Three articles from the original 27 articles were selected based on review of the title and abstract for relevance. Citations were reviewed and 1 additional article was selected. Additional PubMed searches, including search phrases "Botulinum toxin + laryngeal granuloma," "arytenoid subluxation," and "botulinum toxin + rhinitis," were performed with filters for articles published between 2012 and 2022, and "abstract," "free full text," and "full text available," with a total of 25 results, 3 results were selected for inclusion. We excluded 23 based on title and abstract. Two additional references were obtained from an outside search due to lack of information in PubMed on posterior glottic stenosis and cricopharyngeal spasm. A total of 9 articles were included.

Ophthalmology: Eleven articles from the original 27 articles were selected based on review of the title and abstract for relevance. A total of 9 articles were included.

Dentistry: Six articles from the original 27 articles were selected based on review of the title and abstract for relevance. A total of 6 articles were included.

doi:10.36849/JDD.7243e

Cardiology: An additional search was performed using the search phrase "cardiology and botulinum toxin" with filters for publication in the years 2012 to 2022 and "free full text" and "full text available." A total of 37 results were obtained. We excluded 33 based on title, abstract, and article type. A total of 4 articles were included.

Urology/Gynecology: Thirteen articles from the original 27 articles were selected based on review of the title and abstract for relevance. Citations were reviewed and 1 additional article was selected. A total of 14 articles were included.

Adjusted for duplicates, a total of 58 papers from the literature searches and associated references were used for this review. Additional sources were used as needed to supplement information regarding side effects and dosages.

The Medical Applications of Botulinum Toxin

Applications in Dermatology

TABLE 1.

Applications of BoNT in Dermatology
Hyperhidrosis* (Botox,[14])
Bromhidrosis
Chromhidrosis
Frey's syndrome
Eccrine nevus
Granulosis rubra nasi
Compensatory hyperhidrosis
Hidradenitis
Flexural psoriasis
Dyshidrotic eczema
Notalgia paresthetica
Fox-Fordyce disease
Aquagenic keratoderma
Lichen simplex
Idiopathic pruritus
Hailey-Hailey disease
Darier's disease
Raynaud's disease
Alopecia
Keloid and hypertrophic scarring
Folliculitis decalvans
Cutaneous leiomyomas
Rosacea
Post-surgical breast animation deformity

*indicates FDA approval

Hyperhidrosis and Related Conditions

Acetylcholine is a neurotransmitter that plays a key role in both the somatic and autonomic nervous systems. The effect of acetylcholine modulation within eccrine sweat glands is pivotal to the effects of BoNT in treating hyperhidrosis, or excessive sweating. Hyperhidrosis most commonly affects the axillae, palms, and soles. The pathogenesis of hyperhidrosis is due to excessive acetylcholine stimulation of eccrine sweat glands.[15] BoNT has shown effectiveness in reducing both axillary and palmoplantar hyperhidrosis. Botox is currently FDA-approved for axillary hyperhidrosis but used off-label for palmoplantar hyperhidrosis.[12] The recommended administration is 50 U intradermally per axilla. The most common adverse effects include local injection site reactions including pain, bleeding, compensatory perspiration in other regions, pharyngitis, and flu-like symptoms.[14]

Other conditions have shown improvement with BoNT, including bromhidrosis, chromhidrosis, amputee stump hyperhidrosis, Frey's syndrome, eccrine nevus, granulosis rubra nasi, and compensatory hyperhidrosis.[12,15] Frey's syndrome is gustatory hyperhidrosis thought to arise from trauma-induced anomalous regeneration of parasympathetic cholinergic nerves and sympathetic cholinergic receptors.[15] BoNT treatment of Frey's syndrome can induce xerostomia.[10] Hidradenitis suppurativa and flexural psoriasis can both be exacerbated by hyperhidrosis, suggesting a possible utility of BoNT in these challenging and often treatment refractory disorders.

Interestingly, a psoriasiform cutaneous reaction associated with BoNT administration has been reported.[10] This reaction was theorized to occur due to increased innervation and expression of CGRP and substance P in skin affected by psoriasis. BoNT modulates CGRP, substance P, c-fibers, and glutamate, suggesting a role for BoNT in treating psoriasis.[10,15] The paradoxical psoriasiform reaction likely occurred due to dysfunctional neural response to the toxin.

Pruritus and Pain

BoNT may alleviate pruritus through mediation of c-fibers, substance P, and glutamate. This lends utility in conditions such as dyshidrotic eczema, notalgia paresthetica, Fox-Fordyce disease, aquagenic keratoderma, lichen simplex, and idiopathic pruritus.[15] The use of BoNT in acantholytic disorders, including Darier's disease and Hailey-Hailey disease, is limited to case reports, although these were excluded in our review. In Hailey-Hailey disease, flexural acantholysis leads to maceration, erythema, and pruritus exacerbated by heat and sweat. Darier's disease primarily affects areas concentrated with eccrine glands. Likely through mechanisms described above for treating both hyperhidrosis and pruritus, BoNT has been shown to improve symptoms in these conditions.[15]

doi:10.36849/JDD.7243e

The application of BoNT for pain reduction has also been studied in the setting of cutaneous leiomyomas. In studies, BoNT was demonstrated to improve circulation, pain, ischemic ulceration, and cold tolerance in Raynaud's disease.[15,16] Duration of effectiveness has been reported from months to years.[16] It is thought that BoNT inhibits expression of alpha-2 receptors as well as norepinephrine release in a similar mechanism to how it inhibits acetylcholine release. Inhibition of norepinephrine release prevents vasoconstriction.[13,16] BoNT further exerts effects on pain by modulating the activity of nociceptive neurotransmitters including substance P, glutamate, CGRP, and norepinephrine.[16] Temporary hand muscle weakness is the most commonly reported complication of BoNT treatment of Raynaud's; however, patients often report overall improvement in hand functionality when their symptoms are controlled. Injection in neurovascular bundles proximal to the A1 pulley and dosages less than 50 U were associated with lower incidence of weakness. While the neurovascular bundles slightly proximal to the A1 pulley were the most common sites of administration, a wide variety of application locations has been reported in the literature.[16]

Wound Healing and Scars

BoNT may be used therapeutically in improving aesthetic outcomes of post-surgical and wound healing. Through proposed effects on muscular relaxation, reduced perpendicular wound tension, and fibroblast inhibition, BoNT has shown favorable results in minimizing the appearance and texture of hypertrophic scars.[15,17] Kasyanju et al reviewed 6 studies measuring the effect of BoNT-A on surgical scar appearance. These studies included variations on prospective, blinded, randomized, placebo-controlled, and even split-scar designs (1 study met all these criteria). At follow-up (between 6 months and 1 year), all studies showed improved scar appearance when treated with BoNT vs wounds not injected with BoNT. Studies assessed results of BoNT injected immediately after closure, within 24 hours post-closure, within 72 hours post-closure, and within 5 to 9 days post-closure. Interestingly, improvement was noted with varying intervals between wound closure and BoNT injection.

As suggested by the results of the study above, BoNT may also have a critical role in the prevention, not just management, of hypertrophic scarring. The literature is less clear in defining this role, but Kasyanju et al also reviewed 2 studies in which all patients treated with 2.5 IU/cm^3 every month for 3 months demonstrated improvement in their scars at month 6 follow up. In the study by Elhefnawy included in this review, patients not only experienced overall visual improvement of their scars, but also symptomatic improvement of pruritus and erythema.

Kasyanju et al found similar results in the improvement of keloid scarring with BoNT. They reviewed 4 studies, including 1 randomized controlled trial, 1 randomized uncontrolled trial, 1 case study, and 1 clinical letter. Improvement was noted in all studies; however, there was variability in the degree of improvement. In the case study, after 1 injection of BoNT symptoms were improved but no visual change in appearance of the keloid was reported after 5 weeks.[17] In the clinical letter describing a study of 12 patients, 2 patients experienced recurrence of keloid after treatment. Of note, some patients in this study also received intralesional steroid injections during the course of this study.[18] Also of note, in the randomized trial comparing BoNT-A with intralesional steroid as a control, classic side effects of corticosteroids were reported in patients who received the control, but no side effects were reported with the use of BoNT-A in any of the studies.

Only 2 of the studies reported by Kasyanju et al reported side effects with the use of BoNT.[17] Those reported included an asymmetrical smile at 7 days post-treatment of a surgical scar on the philtrum. Further review of the study by Ziade et al revealed that this occurred despite symmetrical injection location and quantity. This event did not impact overall subjective patient satisfaction, which was 100% in the toxin group. Another adverse event in this study was skin flap ischemia, again on the philtrum, which did impact final cosmetic outcomes.[19] Recurrence in nearby areas following the treatment of keloids was reported in the clinical letter.[18] However, keloids are notably treatment refractory, and recurrence is not unexpected. These results suggest that the use of BoNT may serve as an alternative with less risk profile for the treatment of hypertrophic scars and keloids.

BoNT has also shown to reduce graft contraction, inflammation, and fibroblastic activity in full-thickness wounds treated with grafts.[15] Breast animation deformity, associated with disruption of the subpectoral and latissimus dorsi during breast reconstruction and/or augmentation surgery, is another post-surgical complication that can be temporarily improved by BoNT.[2]

Hair Loss

BoNT has been studied in the treatment of several types of alopecia.[2,15] In androgenetic alopecia, benefit is postulated to be through relaxation of scalp muscles and increasing circulation.[2] In folliculitis decalvans, it is suggested to exert results through anti-inflammatory effects.[15]

Rosacea

Another off-label use of BoNT has been in treating severe flushing associated with rosacea. The flushing characteristic of rosacea can be triggered by a variety of stimuli, and BoNT is thought to relieve this reaction through inhibition of cholinergic activity when injected intradermally to the cheeks.[2]

doi:10.36849/JDD.7243e

Applications in Neurology and Psychiatry

TABLE 2.

Applications of BoNT in Neurology
Migraine and headache* (Botox,[14])
Major depressive disorder
Trigeminal neuralgia
Spasticity* (Xeomin,[7] Dysport,[8] Botox,[14])
Cerebral palsy
Bell's palsy
Cervical dystonia* (Botox,[14] Xeomin,[7] Dysport,[8] Myobloc,[9])
Tic disorder/Tourette
Essential tremor
Chronic low back pain/Myofascial pain
Tardive dyskinesia
Notalgia paresthetica
Peripheral neuropathy

*indicates FDA approval

Headache and Migraine

Headache is a very common condition and has several etiologies, subdivided into primary and secondary causes. A primary headache occurs when the main disorder is the headache itself, rather than a secondary etiology causing the headache. Some examples of primary headaches include tension headache, migraine, trigeminal cephalalgia, and nummular headache, whereas a variety of vascular, neurological, or inflammatory processes may result in secondary headache.[20]

Chronic migraines are defined as headaches present for at least 15 days per month and lasting longer than 3 months.[6] Botox (*onabotulinumtoxin A*) is a BoNT preparation that is FDA-approved for prophylactic use in chronic migraine headaches. Studies have shown promising results that BoNT reduces the frequency of migraine headache, intensity, and duration. The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2 trials evaluated the efficacy of BoNT-A in 1,384 patients with chronic migraine. The trials showed a significant reduction in headache frequency, quality of life measurements, total headache hours, and Headache Impact Test-6 Scores.[21,22] Injection sites target branches of the trigeminal nerve, with doses ranging from 155 U to 195 U. Injections were distributed across 31 to 39 sites in the head and neck muscles, which include the procerus, frontalis, corrugator, temporalis, paraspinal, occipitalis, and trapezius muscles.[22]

Patients with chronic migraine may also have comorbid depression and anxiety. Independent studies have shown BoNT also reduces these symptoms, as injection into the glabellar muscles appears beneficial in treating depression.[20] Magid and colleagues performed a literature review of studies that used BoNT-A in the treatment of major depressive disorder. All 5 studies that were included demonstrated a significant reduction in self- and expert-rated depression scores with BoNT-A injection into the glabellar muscles. Side effects experienced by patients included local irritation after injection and headache.[23]

In addition to chronic migraine, BoNT therapy is an off-label therapy for other types of headache including episodic migraine that persist for less than 15 days per month.[20] In treating this condition, several studies have found a benefit in the use of BoNT, which includes reduced frequency of headache, decreased severity, and better satisfaction compared with placebo.[20] On the other hand, other studies including a meta-analysis found no association between BoNT treatment and outcome.[20]

Tension-type headaches are another type of headache for which studies have shown a reduction in symptom intensity with use of BoNT.[20] Treatment outcome may depend on the areas of the head, neck, and back muscles targeted by treatment, the dosage used, and number of treatment cycles.[20] The suggested interval between treatments is 12 weeks, which is a more feasible choice for patient adherence compared with daily intake of analgesic agents.[20]

New daily persistent headache is a subtype of chronic daily headache manifesting as a continuous headache within 24 hours and persisting for longer than 3 months. A retrospective study assessed the benefit of Botox (*onabotulinumtoxinA*) on new daily persistent headaches. The results showed a progressive decrease in headache frequency and severity at months 6 and 12.[20]

Other headache types including cluster, cervicogenic, post-craniotomy, post-traumatic, low-tension, and nummular headaches have shown to benefit from BoNT therapy.[20] However, other studies in the application of BoNT for these types of headaches did not find a clear benefit of BoNT therapy compared with placebo or as an add-on therapy.[20]

Side effects of BoNT in the treatment of chronic migraine include neck pain, progressively worsening migraine, ptosis, and muscle weakness.[14]

Trigeminal Neuralgia

Trigeminal neuralgia is characterized by sudden, brief, intense stabbing pain in 1 or more branches of the trigeminal nerve supplying the face. Episodes may be triggered by facial stimulation, occur multiple times a day, and cause severe distress in the affected patient.[24] Ostrowski and colleagues performed a systematic review highlighting the evidence of therapeutic efficacy of BoNT-A on trigeminal neuralgia. They measured pain scores using the visual analog scale (VAS), which relies on a continuum of subjective measures between no pain and the worst possible pain.[25] Five out of the 7 studies included reported some treatment response to BoNT therapy. Four of

doi:10.36849/JDD.7243e

the studies reported significant differences in pain intensity, symptoms frequency, and VAS scale scores when treated with BoNT compared with placebo groups.[26]

Spasticity

Muscle spasticity typically encompasses a combination of muscle weakness and muscular dysfunction manifesting as dystonia, spasms, or rigidity. Etiologies include cerebral stroke, traumatic brain injury, and multiple sclerosis. Using BoNT in these clinical conditions can reduce muscle tone and pain and improve functionality.[27]

The FDA has approved the treatment of upper limb spasticity in adult patients with Botox (*onabotulinumtoxinA*), Xeomin (*incobotulinumtoxinA*), and Dysport (*abobotulinumtoxinA*) preparations.[7,8,14] Side effects of these preparations vary depending on the population and disease being treated. Botox may cause allergic reactions, symptoms of the eye and eyelid, headache, neck pain, and pain at the injection site.[14] Adult patients with upper limb spasticity reported side effects of Xeomin including seizures, dry mouth, upper respiratory infection, sore throat, and nasal congestion.[7] Common side effects of Dysport include muscle weakness, depression, nasal congestion, dizziness, and musculoskeletal pain.[8]

Xeomin has also been approved for upper limb spasticity in pediatric patients ages 2 to 17 years old with the exclusion of cases with cerebral palsy as the underlying etiology.[7] The most common side effects reported in this population are nasal congestion, bronchitis, and sore throat.[7]

Dysport has been approved for the treatment of spasticity in patients 2 years of age and older. Common side effects experienced in these patients include upper respiratory infection, fever, nasal congestion, sore throat, and flu.[8]

Cerebral Palsy

Cerebral palsy is a medical condition caused by an insult to the developing fetal brain that can affect a variety of musculoskeletal, sensory, cognitive, and perceptive functions. Motor disturbances are a key resulting manifestation and can include spasticity, dyskinesia, and ataxia.[28] BoNT can be used in patients with cerebral palsy to manage focal spasm, dystonia, and hypersalivation.[27]

Cervical Dystonia

Cervical dystonia typically presents as spasms of the neck and shoulder muscles that produce pain and impact head mobility.[27] Cervical dystonia can be further classified as torticollis, anterocollis, retrocollis, and laterocollis. BoNT is the first-line treatment in treating cervical dystonia.[29] Several clinical trials have assessed the use of BoNT in cervical dystonia and have shown BoNT to be an efficacious treatment.[30] FDA-approved formulations for this indication include Botox (*onabotulinumtoxinA*), Xeomin (*incobotulinumtoxinA*), Dysport (*abobotulinumtoxinA*), and Myobloc (*rimabotulinumtoxinB*).[7-9,14] Patients treated with Xeomin for cervical dystonia may experience dysphagia, neck pain, muscle weakness and pain, and pain at the injection site.[7] Dysport may cause muscle pain and weakness, eye problems, dry mouth, headache, dysphagia, fatigue, and difficulty with speech.[8] Common Myobloc side effects in this setting include dry mouth, dysphagia, pain at the injection site, and headache.[9] Lastly, Botox treatment may result in side effects including dysphagia, upper respiratory infection, neck pain, headache, nasal congestion, and flu-like syndrome.[14]

Bell's Palsy

BoNT may also aid in the treatment of Bell's palsy. Injection into the zygomaticus, orbicularis, and risorius muscles improves facial symmetry that has been distorted by Bell's palsy.[12]

Tourette Syndrome

Tourette syndrome is a clinical disorder characterized by various types of tics, which are spontaneous, involuntary movements, twitches, or sounds performed repeatedly. Diagnostic criteria of Tourette syndrome requires 2 or more motor tics and at least 1 vocal tic, with symptoms presenting longer than a year and onset before 18 years of age.[31] The treatment of choice for Tourette syndrome is antipsychotic pharmacotherapy. There are limited data regarding the use of BoNT; available data show that BoNT is most effective in treating focal or dystonic tics associated with Tourette syndrome.[32]

Essential Tremor

Essential tremor is characterized as a rhythmic, usually symmetrical shaking that may be exacerbated by intentional movement. A 38-week open label study by Samotus and colleagues investigated BoNT in the treatment of essential tremor.[33] In contrast to previous evidence, which had relied on fixed dosing regimens, Samotus et al selected muscles to be treated based on kinematic guidance, creating individualized dosing regimens. Twenty-four participants were assessed at weeks 0, 6, 16, 22, 32, and 38. BoNT injections took place at weeks 0, 16, and 32. Multi-joint biochemical recordings were obtained using the Fahn-Tolosa Marin and Quality of Life (QUEST) scores. The Fahn-Tolosa score rates the severity of tremors, writing, and functional disability. QUEST scores are derived from a 30-item rating questionnaire including physical aspects, psychosocial aspects, and communication. In this study, Fahn-Tolosa Marin scores improved significantly from 16.2±4.6 to 9.5±6.3 (P<0.0005) in 38 weeks. QUEST scores also improved in 38 weeks from 40.3±15.8 to 27.8±15.3 (P=0.028).[33]

Myofascial Pain

BoNT has been studied in the treatment of multiple musculoskeletal conditions.[34] Myofascial pain syndrome is a disorder involving muscles and their surrounding fascia, manifesting as well localized pain associated with trigger points.

doi:10.36849/JDD.7243e

While its etiology is unclear, hypersensitivity and inflammatory processes in the muscles have been postulated as contributing factors.[35] Zhang and colleagues conducted a systematic review and meta-analysis to determine the efficacy of BoNT in treating musculoskeletal conditions.[35] In the myofascial pain group, they analyzed 12 studies, and only 3 of 12 showed a benefit of BoNT in treating myofascial pain syndrome. As such, the authors concluded that the pain relief from BoNT was not statistically significant.[35]

Tardive Dyskinesia

Tardive dyskinesia is a psychiatric condition characterized by involuntary movement and typically occurs secondary to antipsychotic medication use.[36] A study by Esper and colleagues examined treatment efficacy of BoNT on lingual protrusion dystonia (LPD).[37] Out of 421 patients with dystonia, 7 had LPD from tardive dyskinesia. These patients were treated with BoNT. Four out of 7 patients demonstrated no treatment response to BoNT, 1 demonstrated mild response, and 2 demonstrated moderate response.[37] BoNT use in patients with tardive dyskinesia has not been extensively studied, although its application may be useful in select cases.

In a single-blinded comparative study by Slotema and colleagues, 12 subjects with orofacial tardive dyskinesia (OTD) were treated for a 33-week duration with BoNT A for 3 sessions. Dosages of BoNT could be increased between sessions until optimum treatment dosage was reached. The severity of symptoms was measured with the abnormal involuntary movement scale (AIMS). The results showed non-significant reduction in OTD severity. Four of the patients required antipsychotic medication adjustment during the study period. However, in patients in whom antipsychotic medication was not modified, a significant reduction was found (P=0.035).[38,39]

Notalgia Paresthetica

Notalgia paresthetica is a condition of unknown etiology characterized by a sensory mononeuropathy that may present as pruritus, paresthesia, burning sensation, and hyper- and/or hypo-esthesia. The condition clinically presents as a dyspigmented skin patch, often in older patients. It is associated with musculoskeletal conditions.

There are limited data on the use of BoNT for notalgia paresthetica. Martina and colleagues performed a systematic review of BoNT use in dermatology.[4] They comment on 1 randomized clinical trial, case reports, and case series. The randomized clinical trial enrolled 20 patients to be treated with Botox (*onabotulinumtoxin A*) or a placebo saline solution. Assessment using the VAS scale showed no significant differences after 8 weeks. Case reports and case series mentioned allude to some improvement of BoNT therapy for notalgia paresthetica. However, more studies are needed to further elucidate its potential use.[4]

Peripheral Neuropathy

There are several subtypes of peripheral neuropathy in which BoNT has been studied, including post-herpetic neuralgia, diabetic neuropathy, phantom limb pain, complex regional pain syndrome (CRPS), carpal tunnel syndrome, occipital neuralgia, phantom limb pain, and post-surgical neuralgia. Trigeminal neuralgia is another type of peripheral neuropathy discussed separately in this section.[40]

Two randomized clinical trials gauging the use of BoNT for post-herpetic neuralgia found symptomatic improvement compared with placebo. In patients with post-surgical neuralgia, randomized clinical trials and case reports describing the use of BoNT across different surgical scenarios have reported a reduction of pain assessed via the VAS scale, along with decreased burning sensation, reduced postoperative analgesic requirement, and persistence of pain relief for several weeks. In diabetic neuropathy, 2 randomized clinical trials and a subsequent meta-analysis report a significant reduction of pain after applying BoNT.[40]

Multiple studies have investigated the effect of BoNT on carpal tunnel syndrome, phantom limb pain, occipital neuralgia, and CRPS. The evidence for the therapeutic effect of BoNT in these conditions is mixed. A randomized clinical trial evaluating the use of BoNT for carpal tunnel syndrome found no significant difference in outcomes compared with the control group. Other studies assessing phantom limb pain, occipital neuralgia, and CRPS report mixed findings without a large enough effect to reach a sound conclusion. More studies are necessary to elucidate the therapeutic effect of BoNT in these conditions.[40]

Applications in Gastroenterology

TABLE 3.

Applications of BoNT in Gastroenterology
Chronic sialorrhea* (Xeomin,[7] Myobloc[9])
Achalasia
Gastroparesis
Anal fissures
Contractile stoma

*indicates FDA approval

While BoNT is currently used therapeutically in gastroenterology, its use for the following conditions is considered off-label. With the exception of chronic sialorrhea, the FDA has not approved the use of BoNT for any gastrointestinal disorders.[13]

Chronic Sialorrhea

Sialorrhea is hypersalivation, which can be caused by excess saliva production or mechanical failure to remove saliva from the oral cavity. It is also referred to as ptyialis or drooling. Chronic sialorrhea can be caused by neurodegenerative and other akinetic disorders impairing swallowing, or can be a side

doi:10.36849/JDD.7243e

effect of certain medications. It can impair social function and lead to aspiration, skin degradation, foul odor, and/or infection. The parotid gland, submandibular gland, and sublingual glands produce saliva in decreasing order of quantity. Current data show that BoNT injections in the parotid and/or submandibular glands are safe and effective for treating sialorrhea through autonomic denervation.[34,41] The use of Myobloc in adults and Xeomin in adults and children for chronic sialorrhea is FDA approved.[7,9] The recommended dosage for Myobloc is 1,500 units to 3,500 units – 500 units to 1,500 units per parotid gland and 250 units per submandibular gland – no more frequently than every 12 weeks. Results typically last 3 months. Adverse side effects include dry mouth, dental caries, and dysphagia.[9] For Xeomin, the recommended dosage for adults is 100 units per session – 30 units per parotid gland and 20 units per submandibular gland – no more frequently than every 16 weeks. For children, the recommended dosage is based on body weight: a 3 to 2 ratio into the parotid and submandibular glands, respectively, with ultrasound guidance, no more frequently than every 16 weeks.[7]

Achalasia

Achalasia is an idiopathic syndrome characterized by motility issues of the lower esophageal sphincter (LES). It results in deranged peristalsis and loss of LES function due to the neurodegeneration of the myenteric nerve plexus of the esophageal wall, namely the loss of nitric oxide releasing inhibitory neurons. In this disorder, the lower esophageal sphincter is unable to relax, making solid food dysphagia a hallmark symptom, often accompanied by regurgitation, heartburn, and chest pain. The standard for treatment is pneumatic balloon dilation or laparoscopic myotomy, but intersphincteric injection of botulinum toxin provides an alternative form of treatment for more severe and stubborn cases. Typically, 80 units to 100 units of Botox or 240 units to 400 units of Dysport are injected into the 4 quadrants of the LES to treat achalasia.[27] One review stated that Botox is reported to be 80% effective – 60% of patients have recurrent dysphagia after 1 year and 80% after 2 years. BoNT is only recommended for patients who are contraindicated for pneumatic balloon dilation or laparoscopic myotomy and as transient relief for acute cases.[42]

Gastroparesis

Gastroparesis (GP) is a syndrome characterized by delayed gastric emptying not caused by outlet obstruction or ulceration. It presents with symptoms including nausea, vomiting, bloating, pain in the upper abdomen, early satiety, and postprandial fullness. Electrolyte replenishment, nutritional support, modifications in diet, and improving glycemic control in diabetic patients comprise first-line treatment of GP. Medications include antiemetic drugs to combat nausea and prokinetic agents like dopamine-receptor antagonists to promote gastric emptying, but they have not proven to cure GP in the long-term. Gastric electrical stimulation and/or pyloromyotomy are more invasive treatments used for more recurrent symptoms. Endoscopic intramuscular BoNT-A injections have been proven to promote pyloric relaxation by inhibiting smooth muscle activity, but further investigation into its efficacy for GP is needed as previous studies have not shown significant difference between treatment with BoNT-A and a placebo.[43]

Anal Fissures

Anal fissures result from tears in the mucosa of the distal anal canal. Complications can result in recurrence, infections, and abscesses. Chronic anal fissures result from hypertonia of the internal anal sphincter which leads to ischemia of the local arterioles. Because anal fissures may also be painful, they reduce quality of life and can lead to impaction of the feces as patients may avoid defecating. While lateral internal sphincterotomy is the most common treatment for chronic anal fissures, it is associated with fecal incontinence.[44] Acute anal fissures can be treated by softening the patient's stool and managing the pain. When those methods fail to heal the fissures and the condition becomes chronic, BoNT-A can be used therapeutically. BoNT injections, a well-established treatment for chronic anal fissures, help relax the internal anal sphincter, allowing for better blood circulation and healing, and reduced pain. There is no consensus on injection site for treating anal fissures with BoNT, but typically 2.5 U to 10 U Botox or 10 U to 40 U Dysport are used.[27]

Contractile Stoma

Stomata are openings in the abdominal wall created during surgery to allow for evacuation of intestinal or bladder contents. Ileostomies and urostomies, in particular, can lead to complications because high liquid output from the small intestine and the bladder can degrade the adhesive material of the pouch and potentially irritate the skin barrier. Pouching system modifications can be made to address the leakages; but if the stomata are hypercontractile, they may periodically shorten to the skin surface level or below, resulting in recurrent pouching system malfunctions or leaks.

One prospective case series concluded that BoNT-A may be an effective form of treatment, as it locally blocked muscle activity, resulting in less contraction of the stomas.[45] Of 10 patients treated with BoNT for either ileostomy or urostomy, 7 reported long-term success in treatment as leakage was reduced and failure of pouching system sealing was resolved. In 2 cases, the injection results were not sustained as these patients may have had neutralizing antitoxin antibodies. The investigators hypothesized that the benefits of BoNT treatment could be attributed to the prevention of longitudinal smooth muscle contractions and thus the effective lengthening of the stomas. There is no consensus on optimal dosage for treatment of contractile stomas with botulinum toxin.

doi:10.36849/JDD.7243e

Applications in Ophthalmology

TABLE 4.

Applications of BoNT in Ophthalmology
Strabismus* (Botox,[14])
Blepharospasm* (Xeomin,[7] Botox,[14])
Alternative to surgical tarsorrhaphy
Keratoconjunctivitis sicca
Entropion

*indicates FDA approval

Strabismus

Strabismus is a condition by which impairment of the ocular cranial nerves or muscles causes a unilateral misalignment of the eyes inward (esotropia) or outward (exotropia). *OnabotulinumtoxinA* is currently FDA-approved to treat this condition in patients greater than 12 years of age, with 1.25 U to 2.5 U as the indicated dose injected into any single muscle for both vertical and horizontal strabismus.[14] The injection relaxes these muscles and promotes realignment of the eye. Adverse effects including retrobulbar hemorrhages have been described, which may impede retinal perfusion and must be recognized.[14]

Although surgery has remained the mainstay treatment, Escuder & Hunter describe the increasing frequency of BoNT use in both adult and pediatric patients in their systematic review.[46] They note 3 different formulations of BoNT with varying biological characteristics and concentrations.The toxin may be diluted down to minimize postoperative complications, such as ptosis and unintended spread of the toxin and subsequent consequences. The use of BoNT was also evaluated in meta-analyses in 2017, identifying a pooled success rate of 76% in pediatric patients with sustained exotropia studies reporting large success rates, especially in patients with minimal deviation.[47]

In fact, blepharoptosis is the most commonly reported consequence of treating strabismus, especially in children.[10] To minimize this, it is suggested to inject 1 cm or more above the supraorbital ridge on the midpupillary line when entering into the corrugator muscles.[10]

Postoperative ptosis may be successfully treated with alpha-adrenergic ophthalmic solutions. Paradoxically, transient strabismus may result following injection, leading to temporary diplopia from weakness of the oblique musculature, but this is potentially easily alleviated by simple eye patching. In addition, specific adverse effects in the periorbital region have been well described, including pseudoherniation of fat pads, lagophthalmos, and loss of orbicularis oculi tone and function. BoNT use in patients with a history of acute angle glaucoma must be cautious, as injection may precipitate mydriasis and subsequent exacerbation.

Blepharospasm

Commonly known as eye twitching, blepharospasm is the abnormal spasm of the ocular musculature often secondary to a neurological condition. As of 1989, both Xeomin and Botox are FDA-approved as the first-line treatment for blepharospasm.[7,14] The recommended initial dose of Xeomin is 25 units per eye, and adverse effects including ptosis, dry eyes, vision loss, and dry mouth have been reported.[7] The recommended initial dose of Botox is 1.25 units to 2.5 units in 3 sites in each affected eye, and similar adverse effects to Xeomin are also well-described, in addition to corneal exposure and ulceration and persistent epithelial defect.[14] Studies have shown success rates of over 90% for these patients using these treatments.[34]

The toxin may be directly injected into the orbicularis oculi muscle every 3 to 4 months as indicated. Dosages may differ depending on the individual patient's requirements. BoNT is also readily available for the treatment of corneal astigmatism, benign eyelid fasciculations, and nystagmus.[12] Growing evidence continues to support its use for these conditions.[13,48]

Alternative to Surgical Tarsorrhaphy

Moreover, BoNT injection has become an alternative to surgical tarsorrhaphy for the treatment of corneal conditions. In the surgical approach, the upper and lower eyelids are moved closer together to cover the eye; and this has been a widely successful treatment method for non-healing epithelial defects, especially in the cornea. In a study by Yucel and Arturk (2012), it took 2.33 ± 1.44 days with peaking at 5.73 ± 2.63 ays to induce ptosis, with a statistically significant improvement in symptoms.[49]

Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca, also known as dry eyes, is also now treatable with off-label use of BoNT. The toxin reduces the frequency of blinking via inhibition of the orbicularis oculi muscle, which thereby minimizes tear drainage from the eye to maintain its moisture.[2] Similarly, the toxin can be used to relax this same muscle to treat symptomatic entropion or the involuntary turning of the eyelid. Paradoxically, however, its use in this manner may accentuate the development of keratoconjunctivitis sicca syndrome, likely due to inhibition of the lacrimation response.[2]

Applications in Otorhinolaryngology

TABLE 5.

Applications of BoNT in Otorhinolaryngology
Allergic rhinitis
Posterior glottic synechiae/stenosis
Cricopharyngeal spasm
Laryngeal granulomas
Laryngeal joint dislocation
Laryngeal dystonia and dysphonia

doi:10.36849/JDD.7243e

Allergic Rhinitis

Allergic rhinitis is an inflammatory reaction mediated by IgE caused by exposure to environmental allergens. Inflammation of the nasal mucosa can cause hypersecretion of the nasal glands, often leading to sneezing, itching, and nasal obstruction. Allergic rhinitis is characterized by these symptoms lasting more than 1 hour for 2 or more days.[50] While there are many forms of treatment for allergic rhinitis, such as nasal decongestants, corticosteroids, and immunotherapy, some patients remain unresponsive to said therapies and still experience rhinorrhea. In terms of the duration and severity of symptoms, BoNT has proven to be superior to steroid injections in 1 randomized control trial (RCT) with 39 patients and, in another RCT, more effective than a saline placebo at reducing rhinorrhea but not congestion.[41] Various clinical studies have shown that nasal symptoms can be relieved by intranasal injection of BoNT, although there is no consensus on the dosage as 40 units to 200 units have been used across those studies.[50]

Posterior Glottic Stenosis

Posterior glottic stenosis (PGS) is a kind of laryngotracheal stenosis with scarring of the glottis or vocal fold fixation. Scarring associated with PGS is often found in the interarytenoid area and may extend to the arytenoids and cricoarytenoid joint. It is most often caused by prolonged or traumatic endotracheal intubation, but can be a result of other trauma or disease, or may be idiopathic. While PGS is difficult to treat and surgeries and stents are typically used, BoNT is used as a supplemental therapy.[51]

Cricopharyngeal Spasm

The cricopharyngeal (CP) muscle is found at the junction between the pharynx and the esophagus and is the major contributor to the upper esophageal sphincter (UES). Cricopharyngeal spasm is 1 cause of UES dysfunction and subsequent issues with swallowing; patients with cricopharyngeal spasm complain of a range of symptoms including globus sensation, dysphagia, and aspiration in more severe cases. Balloon dilation and endoscopic cricopharyngeal myotomy are used as treatment, but BoNT has been an alternative therapy to surgery since 1993. One logistical regression analysis on the efficacy of various treatments for CP dysfunction reported that dosages range from 10 units to 100 units, most being between 5 units and 50 units. They found that while BoNT injections were a safe and effective treatment for CP spasm, balloon dilation was just as effective and myotomy was significantly more effective.[52]

Laryngeal Granulomas

Laryngeal granulomas are non-cancerous lesions that may result from vocal abuse, intubation, and laryngopharyngeal reflux. Granulomas are benign but can recur, and symptoms include globus sensation, cough, and an excessive urge to clear the throat. BoNT is indicated for treatment because it can be used to temporarily paralyze the vocal folds, reducing friction of the arytenoid cartilages and allowing healing.[53]

Arytenoid (Laryngeal) Joint Dislocation

Arytenoid dislocation, also known as arytenoid subluxation, describes the separation of the arytenoid cartilage from the cricoarytenoid joint. It can be caused by trauma or airway instrumentation, such as laryngoscopy or intubation. It is a rare condition that is often mistaken for recurrent laryngeal nerve paralysis, both of which can present with dystonia and dysphagia. When spontaneous recovery may occur, arytenoid dislocation is typically treated with closed reduction under general anesthesia, and BoNT is used as adjuvant therapy.[54]

Laryngeal Dystonias/Spasmodic Dysphonia

Laryngeal dystonia, also known as spasmodic dysphonia (SD), is a vocal cord dysfunction characterized by either hyperadduction or hyperabduction upon speaking, bilaterally or unilaterally, due to spasms of the intrinsic laryngeal muscles.[55] SD can result in glottic or supraglottic airway obstruction, and symptoms include breathy voice (abductor type) and hoarseness (adductor type), most commonly. BoNT is the gold standard for treatment of laryngeal dystonia.[27] Various RCTs have proven the efficacy of Botox as treatment for adductor laryngeal dystonia, but that of abductor type laryngeal dystonias is less well reported.[56] One RCT demonstrated that its use is more effective in more severe cases.[41]

Applications in Dentistry

TABLE 6.

Applications of BoNT in Dentistry
Bruxism
Temporomandibular joint disorders
Mandibular spasm

Bruxism

Bruxism is a common condition described colloquially as "teeth-grinding," which may result in unintended consequences such as headaches, flattening of the teeth, and gum recession in severe cases. It often occurs in patients under increased stress or may result from other underlying causes. The use of BoNT is now indicated for the treatment of this condition by direct injection into the masseter or temporalis muscles. By inhibiting the SNARE protein, BoNT inhibits acetylcholine-mediated muscle contraction.[57] Although 37.8% of dentists in Saudi Arabia would like to use the toxin, it is still met with much resistance, as up to 44% of dentists are still not fully knowledgeable about its indications and side effects.[57] This supports the growing need to inform clinicians around the world about the benefits of using BoNT to treat this condition.

BoNT has also been reviewed at length as a means to treat pathological clenching.[58] By inhibiting masseter contraction in this condition, BoNT can help mitigate the associated trauma to the gingiva, teeth, and other oral structures to promote healing. This is especially useful in promoting faster healing in patients receiving oral or periodontal surgery. The suggestion is

doi:10.36849/JDD.7243e

to use very small doses of the toxin to maximize benefit while mitigating potential risks and lowering the side effect profile of the toxin injection.

Temporomandibular Joint Disorders

Similarly, the toxin is also available as an off-label option to treat other temporomandibular joint disorders (TMJ) due to misalignment of the muscles and bones of mastication. The presentation is similar to that of bruxism, and bruxism is often a key component of TMJ disorders. By eliminating the clenching reflex that is often present in these conditions, BoNT relaxes the muscles well enough to eliminate this negative effect, while maintaining normal chewing and swallowing actions so as not to impair function.[59] Nonetheless, multiple studies emphasize the need for appropriate dosing and injection techniques to minimize complications and maximize the potential benefit of this treatment.[13,34] These studies make mention of the currently unknown optimal dosage; but because other studies discuss the role of smaller amounts of toxin for these purposes, future studies may be warranted to assess optimal dosing. Furthermore, Witmanowski and Blochowiak identify the risk of toxin diffusion to the parotid gland when injected into the masseter, which may result in an unintended decrease of parotid gland secretions and salivary enzymes.[10]

Mandibular Spasm

Similar to bruxism and other TMJ disorders, involuntary spasm of the mandibular muscles is another condition treatable with BoNT. It has been shown that dilution of the 200 units/4 mL dose to a final concentration of 5 units per 0.1 mL is optimal to maximize this benefit.[58]

Applications in Urology and Gynecology

TABLE 7.

Applications of BoNT in Urology and Gynecology
Detrusor instability
Idiopathic detrusor instability
Neurogenic detrusor overactivity* (Botox,[14])
Dyssynergia
Interstitial cystitis
Erectile dysfunction
Benign prostatic hyperplasia
Vulvar pain disorders
Vaginismus
Chronic pelvic pain

*indicates FDA approval

Detrusor Instability

Neurogenic detrusor overactivity (NDO) and idiopathic detrusor overactivity, also called overactive bladder (OAB), are disorders characterized by bladder spasms, urinary incontinence, urinary frequency and urgency, and nocturia. Detrusor external sphincter dyssynergia (DESD) causes urinary retention and difficulty emptying the bladder, which can cause renal damage if left untreated.[60] In the past decade, the FDA has approved the use of Botox to treat NDO, with the recommended dosage being no more than 200 units per treatment session. Side effects include urinary tract infection and urinary retention.[14] As of 2014, the American Urological Association recommends BoNT as a third-line therapy for patients with OAB when behavioral modification and medications, such as anticholinergics, are not effective. While multiple studies have been conducted for the use of BoNT for DESD, further investigation is required as results were mixed.[60]

Interstitial Cystitis

Interstitial cystitis (IC) is characterized by urinary frequency, urgency, dysuria, and chronic pelvic pain classically relieved with voiding.[60] This condition is suspected in the absence of urinary tract infections and once other identifiable etiologies have been ruled out. The pathophysiology of IC is not fully understood but likely involves alterations in the bladder mucosa accompanied by altered sensitivity and peripheral inflammation.[61] BoNT is thought to affect the sensory afferent pathways by inhibiting release of neurotransmitters such as substance P, glutamate, and other neuropeptides.[60] Studies using BoNT for the treatment of IC have shown improvement in overall response, symptom indices, quality of life, increased bladder capacity, decreased pain, and decreased urinary frequency.[62] Furthermore, symptom maintenance was better achieved with successive injections.[62]

Erectile Dysfunction

Another off-label use of BoNT is in erectile dysfunction (ED). In the process of achieving an erection, relaxed cavernosal smooth muscle allows blood flow into the corpus cavernosa. As blood volume increases, the pressure in the penis compresses the adjacent subtunical and emissary veins. This prevents blood outflow, which contributes to achieving and maintaining an erection. This process is dependent upon cavernosal smooth muscle relaxation. When the cavernosal smooth muscle is contracted, it prevents significant blood volume from entering the corpus cavernosa to produce an erection. Without significant blood volume in the corpus cavernosa, an erection cannot occur. Vasculogenic ED occurs as a result of decreased arterial perfusion into the penile tissue or from impaired compression of subtunical and emissary veins.[63] Decreased relaxation of the cavernosal smooth muscle affects the compression of emissary and subtunical veins. Previous human studies have shown that BoNT significantly improves penile systolic velocity and duration of erections, presumably by promoting relaxation of the corpus cavernosa and permittance of increased vascular flow.[63]

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common cause of lower urinary tract obstruction that can have a huge impact on the quality of life of men who are affected.[64] The mechanism of

doi:10.36849/JDD.7243e

effect of BoNT in the treatment of BPH is thought to involve denervation-induced glandular atrophy.[62] The evidence in the literature for the utility of BoNT in treating BPH is often unclear and contradictory. Multiple studies have assessed the effects of BoNT on metrics such as American Urological Association (AUA) symptom score, total prostate volume, maximum urinary flow rates (Qmax), International Prostate Symptom Score (IPSS), and prostate-specific antigen (PSA).[62,65,64]

A systematic review conducted by Mangera et al in 2013 found that newer studies contradict prior investigations that demonstrated more significant results.[65] For example, in a multicenter, randomized double blinded, and placebo-controlled study by Marberger et al in 2013, both BoNT and placebo resulted in improvements in IPSS, transition zone volume, prostatic volume, and Qmax.[62,65] In their study, only 1 subset of patients treated with 200 U of BoNT with a prior history of alpha blocker therapy showed significant improvement in IPSS compared with placebo. Interestingly, the placebo effect was not noted in an earlier placebo-controlled trial by Maria et al.[65,64] A comprehensive analysis by Silva et al showed improvement in urination in BPH patients with urinary retention and indwelling catheters. However, the authors note that there is great heterogeneity in experimental designs and quality across these included studies, which challenges their direct comparison.[65]

Another review article reported that BoNT was shown to improve a number of metrics, including AUA symptom scores, urinary flow rates, IPSS scores, IPSS QoL scores, post-void residual volume (PVR), PSA, and total prostatic volume in a number of studies they analyzed.[62] However, heterogeneity in the injection approach (eg, transrectal, transurethral, transperineal), quantity of BoNT administered, time to effect, magnitude of effect, and overall design between these studies, as well as the contradictory results of the Marberger et al investigation, all demonstrate that further research is needed before definitive conclusions can be drawn.

Side effects of BoNT treatment reported included urinary tract infection, pelvic pain, hematuria, hematospermia, urinary retention, and urosepsis.[62] Notably, in the limited data reported, deterioration in sexual functioning has not been shown as a side effect of intra-prostatic injection of BoNT.[62]

Vulvodynia, Vaginismus, and Pelvic Pain

Vulvodynia is chronic vulvar pain lasting greater than 3 months in the absence of an identifiable primary cause. It is a complex condition that can negatively impact quality of life.[66] BoNT has been studied in the treatment of refractory vulvodynia in several case studies due to its nociceptive inhibitory effects. In 1 study by Pacik, all subjects experienced improvement in pain with variable numbers of injections, ranging from 20 to 40 units of Botox.[15]

When used in conjunction with progressive dilatation, BoNT has shown efficacy in the treatment of vaginismus, which is a type of genitopelvic pain/penetration disorder characterized by involuntary pelvic muscle spasm during attempted vaginal penetration.[15,67] In other studies of patients with vaginismus and vulvodynia, BoNT has shown similar results in increasing patient quality of life and reducing both pain and use of analgesics.[68]

A retrospective cohort study of female patients treated with infralevator BoNT for refractory myofascial pelvic pain showed improvement in pain and reduced urinary incontinence.[68] BoNT was injected into the major pelvic floor muscles, and injection sites were selected based on patient-provided pain scores and physical examination findings. Side effects seen after treatment in this study included constipation, tenesmus, urinary retention, and fecal incontinence, with all noted adverse reactions resolving spontaneously. These results were consistent with previously reported outcomes in the literature. Similar to its application in treating spasticity in neurological disorders, BoNT's antispasmodic effect on the pelvic floor results in a reduction in pelvic floor muscle pressure. BoNT-induced pelvic floor relaxation has also been associated with improvement in non-menstrual pelvic pain and dyspareunia.[68]

Applications in Cardiology

TABLE 8.

Applications of BoNT in Cardiology
Atrial fibrillation
Hypertension

The potential use of BoNT in cardiovascular conditions such as atrial fibrillation and hypertension has been reported in the literature. The heart is highly innervated and influenced by the central nervous system, extrinsic intrathoracic ganglia, and intrinsic cardiac nervous system (ICNS).[69]

The ICNS contains several ganglionated plexi (GPs) in the epicardial fat pads and muscle of the heart which send and receive information that regulates cardiac contractility, vasomotor tone, and electrical conduction. The major GPs are the right atrial GP (RAGP), inferior vena cava-inferior atrium GP (IVC-IAGP), left inferior GP, left superior GP, and ligament of Marshall tract.[69]

Atrial fibrillation may be triggered by aberrant vagal stimulation. Prior studies, including animal studies, have suggested that botulinum toxin may decrease vagal stimulation and therefore the incidence of postoperative atrial fibrillation (POAF). However, the precise mechanism by which BoNT exerts its effects is not fully clear.[71]To characterize this further, Waldron and colleagues performed a randomized trial to determine the impact of BoNT in (POAF) in 130 adults receiving cardiac surgery. Results

doi:10.36849/JDD.7243e

showed that 36.5% of patients treated with BoNT developed POAF compared with 47.8% of patients receiving a placebo. There was no significant difference in length of hospital stay.[72]

Another randomized trial by Pokushalov and colleagues evaluated the efficacy of BoNT in preventing atrial tachyarrhythmias. Patients with a history of paroxysmal atrial fibrillation undergoing coronary artery bypass surgery (CABG) received BoNT injection into epicardial fat pads or a placebo. Patients were followed for 1 year, which revealed a significant decrease in the incidence of atrial fibrillation in the BoNT-treated group compared with the placebo group.

Romanov and colleagues continued monitoring post-CABG patients treated with BoNT or placebo for 3 years using loop recorders. At the end of the 3 years, the BoNT treatment group had a lower incidence of atrial fibrillation compared with the placebo group.[73]

There is less literature available on the treatment potential of BoNT in hypertension, as only case reports have been described in this setting.[74] Although these individual patients showed improvement, randomized controlled studies are warranted to optimize the potential benefits of BoNT in treating hypertension in the larger population.

DISCUSSION

To date, the FDA-approved, non-cosmetic indications for Botox are urge incontinence, migraine prophylaxis, limb spasticity, cervical dystonia, strabismus, and blepharospasm.[14] Xeomin is indicated for chronic sialorrhea in patients older than 2 years of age, upper limb spasticity not due to cerebral palsy in adults and pediatric patients 2 to 17 years old, cervical dystonia in adults, and blepharospasm in adults.[7] Dysport is indicated for spasticity in patients older than 2 years of age and cervical dystonia in adults.[8,75] Finally, Myobloc is indicated for cervical dystonia and chronic sialorrhea in adults.[9]

The side effects reported for cosmetic uses of BoNT are typically mild, self-limited, and transient. Localized cutaneous reactions are common and include swelling, erythema, ecchymoses, hematoma, pain, infection, and sensory disturbance, as well as headache, adverse or unintended aesthetic outcomes, and hypersensitivity reactions. Most of these can be prevented with judicious administration by professionals well-versed in anatomy and technique. Application of ice and pressure, as well as minimizing anticoagulant factors can minimize bruising. Topical anesthetic preparations and diluting with saline with a higher pH due to preservatives can reduce pain. Infection can be prevented with appropriate antisepsis. Headache may occur due to stress, muscle spasm, breach of the periosteum, and muscle hematoma.[10] Distribution of BoNT beyond its intended target muscles can result in both functional limitation and aesthetic dissatisfaction. Specific examples of functional ophthalmic complications have been discussed in the relevant section.[10]

Numerous cosmetically displeasing adverse effects have been reported including changes in eyebrow appearance, facial asymmetry, increase in prominence of untreated rhytides, and sunken or paradoxical bulging appearance. Disturbances affecting the perioral and masseter area can also manifest as functional limitation. This may be of particular concern in certain lifestyle activities, such as singing, scuba diving, or wind instrument playing. Notably, most of these aesthetic concerns are self-limited and may be treated with additional administration of BoNT if distressing.[10]

Specific side effects of particular non-cosmetic applications have been discussed in their respective sections. It is reported that non-cosmetic applications have a 33 times higher frequency of serious adverse effects. This may be due to the higher dosages typically used in therapeutic use of BoNT.[10] In general, serious adverse effects of BoNT include severe hypersensitivity reactions and signs of systemic botulism. There are no differences in occurrence of anaphylactic reactions between cosmetic and therapeutic BoNT.[10] There are numerous theories posited to explain systemic BoNT toxicity, but ultimately its pathogenesis is unknown.

Treatment of systemic botulinum toxicity includes supportive care, antitoxin administration, and neurotrophic agents.[10] Ultimately, prevention is key in careful selection of treatment agents, volumes, intervals, dilution, and overall risk-benefit analysis.[10]

Botox is the only formulation to report rare cardiovascular events associated with treatment.[6,14] All agents pose a theoretical risk of transmission of infectious diseases with agents containing human albumin.[7,8,9,14,75] Dysphagia, dystonia, and dysphonia have also been reported as more serious sequelae of BoNT administration, particularly in the treatment of the neck and cervical areas. These areas are predisposed towards dissection of the toxin beyond fascial planes into unintended target muscles. Of note, muscle weakness, dysphagia, and hypersensitivity reactions have been reported with the use of cosmetic BoNT.[10] Other serious adverse effects of cosmetic BoNT include Grave's eye disease, sarcoid granuloma, aneurysm of the superior temporal artery, and respiratory depression.[10]

BoNT is contraindicated in patients with infection at the injection site, known impaired neuromuscular activity, known hypersensitivity reaction, and patients on certain medications. BoNT is also a Category C medication, therefore it is contraindicated in pregnancy and breast-feeding.[7,8,9,14,75] Dysport in particular is contraindicated in patients with a cow milk protein allergy.[75]

doi:10.36849/JDD.7243e

CONCLUSION

Beyond its established uses in cosmesis, BoNT is a relatively safe and versatile neuromodulatory treatment for a variety of disorders system wide. It is already FDA-approved for some of these applications, but others remain in need of further investigation to build upon the promising existing data and harness the full potential of this powerful neurotoxin.

DISCLOSURES

The authors have no disclosures or potential perceived conflicts of interest and/or support, financial interests, or patents to report.

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March 2024 188 Volume 23 • Issue 3

CASE REPORT

Journal of Drugs in Dermatology

Novel Clinical Applications of Topical Ruxolitinib: A Case Series

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ABSTRACT

Topical ruxolitinib, a potent Janus kinase (JAK) inhibitor, has shown significant efficacy in treating inflammatory skin conditions. While its use has already been established in atopic dermatitis and vitiligo, recent reports suggest its potential efficacy in treating other dermatoses. Specifically, topical ruxolitinib may be an effective treatment option for refractory dermatological conditions that are inflammation-driven with dysregulated activity of cytokines implicated in the JAK/STAT pathway. In this case series, we present four novel clinical applications of topical ruxolitinib in treatment-resistant dermatological conditions. These cases include pediatric lichen sclerosus et atrophicus, morphea, perioral dermatitis, and notalgia paresthetica. All four patients reported noticeable symptomatic improvement and a significant improvement in the condition of their skin lesions. Our results suggest that ruxolitinib cream can successfully manage these conditions and may serve as supporting evidence for its formal evaluation.

J Drugs Dermatol. 2024;23(3)::188-190. doi:10.36849/JDD.7696

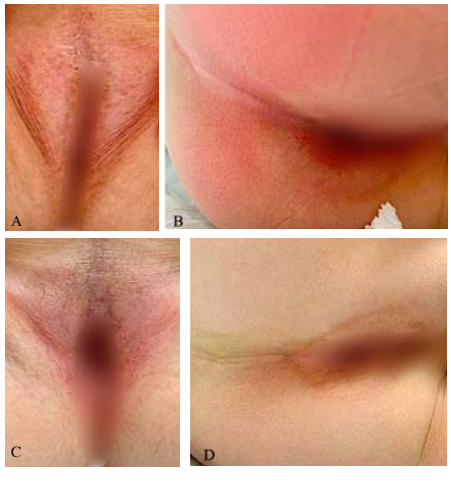
INTRODUCTION

Topical ruxolitinib is a potent Janus kinase (JAK) inhibitor that has demonstrated significant efficacy in treating an array of inflammatory skin conditions. While topical ruxolitinib has been most extensively studied in atopic dermatitis and vitiligo, recent reports have suggested its potential in treating other dermatoses. In this case series, we present four cases of refractory dermatological conditions that were successfully managed with topical ruxolitinib. These conditions include pediatric lichen sclerosus et atrophicus, morphea, perioral dermatitis, and notalgia paresthetica.

Case 1

A 9-year-old female presented with 6 years of recurring pruritic vaginal lichen sclerosus et atrophicus associated with occasional dysuria. Previously failed therapies included high potency topical steroids, crisaborole, and tacrolimus ointment. On exam, there was atrophy and hypopigmentation of the labia majora and minora with an erythematous patch extending from the vagina to the anus (Figure 1 A, B). Ruxolitinib 1.5% cream was applied to the affected areas twice daily for 6 weeks. On follow-up, the erythematous patch was significantly improved and the patient reported notable symptomatic improvement of both her pruritus and dysuria (Figure 1 C, D).

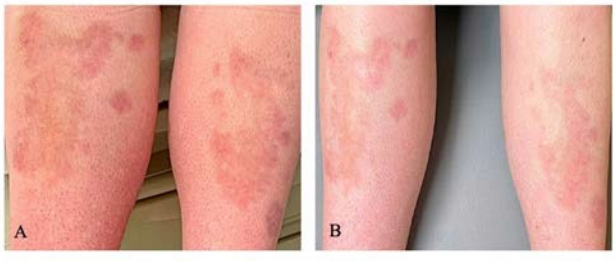
FIGURE 1. Lichen sclerosus atrophicus before and after treatment with topical ruxolitinib.



Case 2

A 13-year-old female with poorly controlled insulin-dependent diabetes mellitus presented with biopsy-proven morphea of the anterior lower legs, which had been present for years. Previously failed therapies included topical clobetasol and

FIGURE 2. Morphea of the legs before and after treatment with topical ruxolitinib.



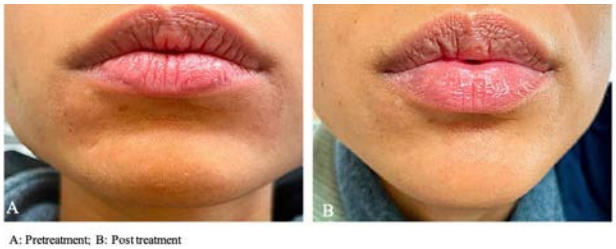
A: Pretreatment; B: Post treatment

calcipotriene. Her lesions were pruritic, and a skin exam revealed depressed hyperpigmented plaques on the bilateral shins with violaceous edges of the superior border (Figure 2 A). Ruxolitinib 1.5% cream was applied to the affected areas twice daily. She returned 6 weeks later with notable improvement of her itch, discoloration, and erythema (Figure 2 B).

Case 3

A 26-year-old female presented with 8 years of chronic, persistent perioral dermatitis. A biopsy of the area demonstrated spongiotic dermatitis consistent with contact dermatitis or an eczematous reaction. Patch testing revealed irritants of parabens and propolis, and these products were subsequently avoided with persistence of the rash. Previously failed treatments included topical tacrolimus, ketoconazole, pimecrolimus, desonide, crisaborole, nystatin, and hydrocortisone. Following the application of ruxolitinib 1.5% cream to her chin twice daily, she returned 2 months later with a resolution of the perioral dermatitis (Figure 3 B).

FIGURE 3. Perioral dermatitis before and after treatment with topical ruxolitinib.



A: Pretreatment; B: Post treatment

Case 4

A 72-year-old female with a past medical history of HIV (viral load undetectable) presented for the evaluation of pruritic notalgia paresthetica. She failed treatment with topical triamcinolone and lidocaine patches. Ruxolitinib 1.5% cream was applied to the affected areas twice daily along with camphor-menthol and amlactin lotions. She returned 6 weeks later with symptomatic improvement of the itch. The patient later reported that she abruptly stopped the treatment, and her pruritus returned.

DISCUSSION

The landscape of dermatologic intervention has evolved significantly in recent decades with the advent of new biologic modalities and molecularly targeted therapeutics. Specifically, the emergence of the Janus kinase (JAK) inhibitor drug class is revolutionizing the treatment of various inflammatory dermatoses. JAKs are non-receptor tyrosine kinases that are pivotal to cellular signal transduction and the downstream cytokine-mediated response.[1] Affected cytokines include interferon (IFN)-γ, IFN-α, interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, IL-21, IL-5, IL-6, IL-12, IL-13, and IL-23.[2] Cytokine-receptor binding results in intracellular JAK dimerization and activation, which subsequently results in STAT protein dimerization and phosphorylation.[2] This ultimately leads to signal transduction to the nucleus and activation of gene transcription.[2] There are 4 different members of the JAK family and 7 different members of the STAT family.[2] As such, numerous distinct inflammatory dermatoses converge on the JAK-STAT pathway, making it an attractive target for inhibition.[2]

Ruxolitinib, a selective JAK1/2 inhibitor, has shown promising results in the treatment of inflammatory skin conditions. Although it was initially developed as an oral medication, topical preparation has significantly improved its safety profile and efficacy in localized treatment.[1] Moreover, as a steroid-sparing agent, it is an appealing option for conditions requiring long-term topical treatment.

In the presented case series, topical ruxolitinib successfully treated four distinct dermatoses: lichen sclerosus et atrophicus, morphea, perioral dermatitis, and notalgia paresthetica. These conditions result from dysregulated activity of specific cytokines and interleukins, which can be targeted by JAK/STAT inhibition.

In lichen sclerosus, studies have found that there is an abnormal activation of the Th1 autoimmune response in affected tissue. This leads to the upregulation of pro-inflammatory cytokines and immune mediators such as IL-1, IL-7, IL-15, IFN-γ, TNF-α, IL-2 receptor (CD25), caspase-1, ICAM-1, and CD11a.[3] Though its exact pathogenesis is unclear, it appears that blockade of the Th1-predominant inflammatory cytokine cascade can interrupt the faulty collagen production associated with the condition.[3] Additional studies implicate IL-4 and transforming growth factor (TGF)-β resulting in fibroblast activation, altered collagen production, and fibrosis.[4] Ruxolitinib's targets include IFN-γ, IL-2, IL-4, IL-7, and IL-15, which may elucidate its efficacy in this disease process. Moreover, there have been reports of the effective treatment of cutaneous lichen planus with topical ruxolitinib.[5] In an open label study, ruxolitinib effectively reduced clinically apparent lichen planus and downregulated interferon-stimulated genes. Specific cytokine targets of ruxolitinib, such as STAT1, were elevated in diseased tissue and normalized in

responsive tissue.[5] Due to the clinical and pathogenic overlap between lichen sclerosus and lichen planus, it may be possible to extrapolate ruxolitinib cream's efficacy in lichen sclerosus from its success in lichen planus.

Morphea, like lichen sclerosus, may be considered an inflammatory-driven fibrosis.[3] In morphea, increased collagen deposition and fibrosis result from dysregulated cytokines including TGF-β, IL-1, IL-4, IL-6, IL-8, and IL-13.[6] In a case presentation of generalized deep morphea, tofacitinib, an oral nonselective JAK inhibitor, successfully halted disease progression and reversed prior pathology.[7] The authors posit that tofacitinib's blockade of IL-4 interrupted the TGF-β-induced, JAK-dependent fibrosis important to morphea pathogenesis.[3] Ruxolitinib cream similarly inhibits IL-4, which may have contributed to its success in improving the appearance of plaque morphea in our patient. Moreover, ruxolitinib inhibits additional implicated cytokines such as IL-6 and IL-13.

Perioral dermatitis may be considered on the spectrum of atopic skin disease with impaired skin barrier function.[8] Since topical ruxolitinib has already demonstrated efficacy in atopic dermatitis through its suppression of cytokines such as IL-4 and IL-13, its extension to perioral dermatitis may be reasonable. A recent case presentation demonstrating significant improvement in refractory seborrheic dermatitis with topical ruxolitinib provides further evidence for the efficacy of ruxolitinib in treating atopic-associated dermatoses with spongiotic histopathology.[9]

The pathogenesis of notalgia paresthetica is neuropathic, but patients often present to dermatologists with intense pruritus resulting in secondary cutaneous lesions. Thus, targeting the pruritus results in significant symptomatic relief for patients. Though itch pathogenesis is not well defined, IL-4 has been shown to increase neuronal responsiveness to pruritogens via JAK1 phosphorylation.[10] IL-13 is associated as well.[10] Ruxolitinib cream has already proven successful in itch reduction in conditions like atopic dermatitis.[10] The successful amelioration of the pruritus in notalgia paresthetica may be by similar mechanism through its IL-4 and IL-13 blockade.

Our case series may serve as supporting evidence for the pursuit of the formal evaluation of topical ruxolitinib in lichen sclerosus, morphea, perioral dermatitis, and notalgia paresthetica. Of note, though these represent four distinct dermatologic conditions, investigation into their pathogenesis revealed IL-4 dysregulation as a commonality. Formalized clinical studies are necessary to establish its efficacy and safety in these conditions. Further research could unveil a deeper understanding of the mechanisms underlying topical ruxolitinib's therapeutic effect, which could potentially reveal new applications for its use.

DISCLOSURES

Alice B. Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and Xbiotech and has received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine). All other authors have no conflicts to disclose.

ACKNOWLEDGMENT

We would like to acknowledge the patients who agreed to participate as the subjects of this case series.

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doi:10.36849/JDD.8091

March 2024 192 Volume 23 • Issue 3

CASE REPORT

Journal of Drugs in Dermatology

First Use of Combination Oral Deucravacitinib With Tapinarof Cream for Treatment of Severe Plaque Psoriasis

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ABSTRACT

Plaque psoriasis is a chronic, immune-mediated, cutaneous, and systemic inflammatory dermatosis. Its pathogenesis involves the dysregulation of the interleukin (IL)-23/IL-17 signaling pathway. There are a range of treatment options available, encompassing topical agents, biologics, oral systemic therapy, and phototherapy. The utility of combination treatment has also been described and is a budding field of research. Here we describe the first case of adult severe generalized plaque psoriasis treated with once-daily oral deucravacitinib 6 mg combined with tapinarof cream 1% applied once daily. To our knowledge, the combination of these agents has not yet been described in the literature.

J Drugs Dermatol. 2024;23(3):192-194. doi:10.36849/JDD.8091

INTRODUCTION

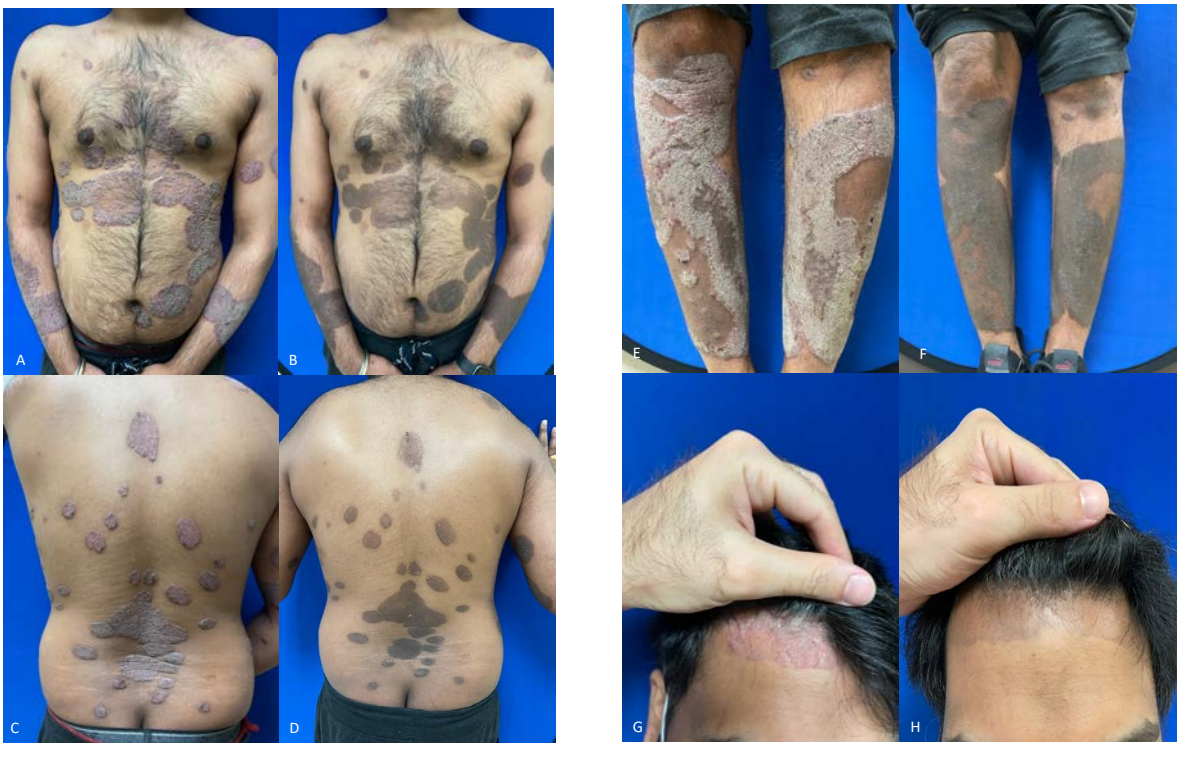
Plaque psoriasis continues to be a great disease burden in the United States. Incidence and prevalence rates of plaque psoriasis are estimated to be 63.8 per 100,000 person-years overall and 3.0% in adults aged 20 years or older, respectively.[1,2] Advances in both systemic and topical therapeutics have ushered in an era of safe non-steroidal options for many patients. Furthermore, as the treatment armamentarium becomes larger, combination therapies involving a systemic medication combined with one or more topical therapeutics will become mainstay.[3] Here we report the first case of generalized plaque psoriasis treated with once daily oral deucravacitinib combined with tapinarof cream 1%.

CASE

A 37-year-old Indian male presents with 3-year history of plaque psoriasis. Deep red to violaceous nummular well circumscribed micaceous plaques with scale covered over 50% of his body surface area (>50% BSA) including the scalp, trunk, extremities and intertriginous areas including the groin, and axillary vaults (Figure 1). He denied any joint pain and personal or family history of cardiovascular disease. He was also treatment naïve having never tried any topical or systemic therapeutics aside from over-the-counter emollients.

Given the patient's frequent travel between India and the United States, his logistical need to carry pills rather than injections, and his desire for a systemic medication with a short half-life so he is able to obtain live vaccines on shorter notice than biologics, we initiated oral deucravacitinib 6 mg once daily. We also initiated tapinarof cream 1% which was applied to the affected areas once daily for synergy. At his 4-week follow-up visit, a significant therapeutic effect was noted with over 75% clearance (Figure 1). Post-inflammatory hyperpigmentation was noted at all sites. Of note, the patient endorsed a transient mild muscle ache in his legs two weeks into treatment that self-resolved prior to his week 4 follow-up visit. Laboratory evaluation of serum creatinine phosphokinase (CPK) at week 4 was within normal limits.

FIGURE 1. (A, C, E, G) Generalized plaque psoriasis affecting the (A) trunk, (C) back, (E) legs, and (G) scalp. (B, D, F, H) Psoriasis-involved areas 4 weeks after combination treatment with oral deucravacitinib 6 mg once daily and tapinarof cream 1% applied to affected areas once daily.



DISCUSSION

Psoriasis is a chronic, immune-mediated inflammatory dermatosis that is estimated to affect more than 7.5 million people aged 20 years or older in the United States.[2] Its pathogenesis is multifactorial; it begins with the activation of myeloid dendritic cells which subsequently secrete interleukin (IL)-12 and IL-23.[4] IL-23 fosters the expansion of Th17 and Th22 cells which together secrete IL-17, IL-22, and TNF-α.[4] Aberrant IL-23/IL-17 signaling is considered the main pathogenic pathway in psoriasis.[4] Thus, therapies that modulate this pathway have been proven to be effective in treating the disease.[4] Furthermore, agonism of aryl hydrocarbon receptor (AhR), which falls outside the aforementioned canonical "psoriasis funnel," results in the indirect reduction of IL-17,[5] as further expounded upon below.

Deucravacitinib is an oral, selective tyrosine kinase 2 (TYK2) inhibitor that works by binding to the pseudokinase domain of TYK2, allosterically inhibiting the activation of STAT-dependent pathways and subsequent IL-12, IL-23, and Type I and III interferon responses.[6,7] A phase 2, double-blind placebo-controlled trial proved the superiority of daily oral deucravacitinib 6 mg compared to control in adult patients with moderate-to-severe plaque psoriasis as evidenced by significantly (P<0.001) higher achievement of at least 75% reduction of psoriasis and severity index (PASI-75) in the treatment group by week 12.[7] This was confirmed by the pivotal phase 3 double-blind, randomized, controlled POETYK PSO-1 and PSO-2 trials which not only proved the superiority of 6 mg oral deucravacitinib daily to control but also to oral apremilast.[6,8]

Tapinarof is a first-in-class topical AhR agonist.[5] AhR acts in a ligand-specific manner and is expressed by a variety of cell types.[5] In the skin, AhR pathways maintain skin homeostasis through immunomodulatory, anti-oxidative, pigmentary, and barrier-protective effects.[5] AhR activity in psoriasis is likely influenced by multiple mechanisms dependent upon the binding ligand.[5] It can influence psoriasis through two main pathogenic arms: immunologically and physically. Immunologically, AhR signaling regulates the differentiation of Th17 and Th22 cells in addition to IL-17 and IL-22 production.[5] Physically, AhR signaling modulates keratinocyte function and skin barrier strength, the dysregulation of both of which have been implicated in the pathogenesis of psoriasis.[5] Indeed, the phase 3 double-blind, randomized, vehicle-controlled studies (PSOARING 1 and 2) both found that once-daily application of tapinarof cream 1% was significantly (P<0.001) more effective in treating mild-to-severe plaque psoriasis than vehicle cream as evidenced by statistically significantly greater physician global assessment (PGA) responses.[9]

Deucravacitinib and tapinarof are two recently FDA-approved medications added to the psoriatic treatment armamentarium. Although each has been proven to be effective in treating psoriasis separately, there have been no reports of the effects of combined usage of these agents. With respect to the patient reported here, plaque psoriasis involved over 50% of his BSA. Pharmacokinetic (PK) studies of tapinarof cream 1% applied once daily for 29 days in adult psoriasis patients with cutaneous surface area involvement up to 46% found limited systemic absorption and lower tapinarof plasma concentration on day 29 than day 1.[10] Given the limited systemic absorption despite high BSA involvement, along with the long-term 52-week safety profile from the PSOARING-3 trial, we implemented tapinarof cream into his treatment regimen.[11] Oral deucravacitinib was also chosen as the systemic medication of choice given its half-life of 8-15 hours which allows for flexibility in dosing given the patient's lifestyle needs for vaccinations and travel.[12] Furthermore, rhabdomyolysis and elevated CPK are listed potential adverse events of deucravacitinib.[13] While the patient noted a mild transient muscle ache in his legs not related to physical exertion, it had self-resolved prior to his 4-week follow-up appointment and his serum CPK level was within normal limits.

Thus, we present the first report of oral deucravacitinib combined with the topical non-steroidal therapeutic tapinarof cream 1% for the treatment of severe plaque psoriasis. This combination resulted in rapid (4 weeks) clearance of severe psoriasis (>50% BSA) in a young adult skin of color patient. To date, no reports have emerged investigating deucravacitinib with a non-steroidal topical agent. This is a unique, multimodal approach to severe plaque psoriasis which we hope will shape future therapeutic strategies.

DISCLOSURES

LK and NTI are paid consultants and speakers for Dermavant Sciences. NTI is a paid consultant and advisor for Bristol Myers Squibb.

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doi:10.36849/JDD.7780e

March 2024 e79 Volume 23 • Issue 2

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Microneedling for Treatment of Acne Scars: Considerations on the Successful Management of This Aesthetic Procedure

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Microneedling is a minimally invasive procedure for treating acne scars which has already been well-established, but it has been reborn in recent years because of innovative findings. It presents many advantages in comparison with other techniques more frequently used such as laser resurfacing and deep chemical peelings; in particular, it consents to achieve good or excellent results with a minimal time (2-3 days) of recovery and rare complications, even in dark phototypes.1,2 It is possible to improve the cosmetic results of severe scarring further with the transdermal delivery of drugs such as vitamins, hyaluronic acid, and platelet-rich plasma (PRP). Additionally, combining these with other aesthetic procedures such as peelings, lasers, and fillers, following an appropriate "wash out" period from microneedling, dermatologists can further optimize results.[3]

Microneedling breaks the compact collagen bundles of scarring in the upper dermis preserving the epidermal barrier function and stimulates the production of new collagen and elastin (as various histological stainings can demonstrate) through the release of cytokines and growth factors by inflammatory process; besides, the creation of deep microchannels permits the transdermal drug delivery. On the contrary, lasers, and in particular ablative lasers break the epidermal barrier with thermal damage and perilesional necrosis so that the times of recovery are longer and side effects are more probable.

More rarely, this technique has been preferred to the traditional aesthetic procedures for treating other scars (surgical, post-traumatic, burn), skin photoaging, and rhytides. In exceptional cases, it has been proven for treating striae distensae and skin laxity with good results.

Of course, contraindications to this aesthetic procedure are active acne, immunosuppression, local infection, keloid predisposition, etc. A prophylactic treatment with oral antiviral drugs for one week can be necessary in cases of a positive history of herpes labialis. Oral anticoagulant drugs have to be interrupted for one week (3 days before and 3 days after the treatment) with this mini-invasive aesthetic procedure.

The first consideration for a successful microneedling is topical anesthesia. Generally, the application of a cream based on 2.5% lidocaine and 2.5% prilocaine under occlusion for 60-90 minutes is suitable before treating acne scars with needles long less than 2 mm; rarely, it can be used topical anesthesia with 30% lidocaine cream for shorter times such as 20-30 minutes and no occlusion, even for more severe scarring. It sets a trend to use a self-occluding topical anesthetic mixture (7% lidocaine and 7% tetracaine) for 30-60 minutes because of its advantages in terms of efficacy and safety.[4]

The second consideration concerns some useful technical suggestions during the operative procedure.[5] Manual roller devices ("dermaroller") are easier to manage in large areas, while electric-powered pen devices ("dermapen") can be preferred in small areas because of the adjustable speeds of the latter; both of them can be combined. These manual devices are more successful when compared with other energy-based instruments such as fractional radiofrequency (FMR) or light-emitting diode (LED) devices[6] because of the thermal damage for the energy dispersed in the superficial skin by the last ones. The sterile steel needles more frequently used for treating acne scars are thin (30-32 G) and 1.5-2 mm in length to enter the superficial dermis; rarely, needles of 2.5-3 mm in length have been suggested for deep acne scars using only this topical anesthesia. On the contrary, needles of 0.5-1 mm in length are preferable for delicate cosmetic areas of the face such as eyelids or lips, especially for treating skin photoaging and rhytides. The density of the needles can also vary according to the different models of dermarollers in Europe and the USA. The operative procedure is standard and consists of 3-4 soft perpendicular passages of the dermaroller over acne scars in 4 directions (12-16 passages) until fine pinpoint bleeding; later on, the application of ice water-soaked sterile gauzes for a few minutes permits to achieve hemostasis.[7,8]

The third consideration is essential to obtain the best results without complications (dyspigmentation, granuloma, scarring). During the first phase post-treatment, erythema, edema, and

doi:10.36849/JDD.7780e

pain are normal and disappear within 2-3 days. Gel based on hyaluronic acid, vitamins, or growth factors (PRP) has to be applied after the treatment. This cosmetic application has to be repeated daily, preferably in the evening, on the facial unit treated for 7-10 days. Sunblock SPF 50+ has to be applied, preferably in the morning, on the face for 7-10 days too. The best results with scarring improvement of 50-75% in most of the patients and over 75% in a small percentage of the patients can be assessed using various grading scales, even if the Goodman and Baron qualitative and quantitative system is the most frequently used.[9] According to most of the studies, these results are comparable with those obtained through non ablative lasers and even fractional ablative lasers. They can be achieved with a different number of sessions of microneedling varying from 1-4 to 6-8 according to the subtype and severity of scarring beyond the age of patients and duration of scarring; in fact, the most patients present mixed subtypes of scars with boxcar and rolling scars which show a greater degree of improvement than ice pick scars. It is useful to apply microneedling at 4-week rather than 2-week intervals[10] as well as to evaluate the final result after at least 3 months from the last session and better after a long follow-up (6-12 months) according to the slow times of a complete neo-collagenesis.[6]

The final consideration concerns the possibility of combining microneedling with other traditional aesthetic treatments for acne scars such as lasers, peelings, fillers, subcision, RF, and so on. This combination can be suggested in selected cases of severe acne scars to improve the aesthetic results achieved with microneedling alone, but it can also increase the risk of possible complications, especially in dark phototypes. The best association is microneedling with fillers such as PRP or similar drugs[11] rather than deep peelings or lasers, preferably after a long follow-up from the last session of microneedling when the process of neo-collagenesis has almost been completed. However, combining microneedling with the transdermal delivery of topical cosmetic drugs since the initial session can prove beneficial, enhancing the ultimate aesthetic results.[12]

In conclusion, microneedling remains a well-established low-cost aesthetic procedure of first choice for the treatment of acne scars[13] in all phototypes[14,15] compared to the most traditional lasers or peelings because it has high efficacy and safety with minimal post-treatment recovery rates and risk of complications. Besides, particular recommendations before the treatment, intra-operative, and after the treatment according to a standardized protocol can optimize the final aesthetic results reserving the combination with more traditional therapies to selected severe cases.[16,17]

DISCLOSURES

The author has no conflicts of interest to declare.

ACKNOWLEDGMENT

Thanks to Prof. K Fritz* for his scientific support in the publication of this manuscript.

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This work has been presented at the SIME (Italian Society of Aesthetic Medicine) Annual Congress 2023 (19-21th May, Rome, Italy) and will be updated at the SIDCO (Italian Society of Surgical and Oncologic Dermatology) Annual Congress 2024 (11-13th April. Sanremo, Italy).

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doi:10.36849/JDD.7558e

March 2024 e81 Volume 23 • Issue 3

CASE REPORT

Journal of Drugs in Dermatology

Urticaria Pigmentosa Without Pruritus

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ABSTRACT

Mastocytosis is a group of disorders characterized by the pathologic accumulation of mast cells in various tissues. One example of mastocytosis is urticaria pigmentosa, which presents with mastocytomas that can cause hives and, when irritated, pruritus. To our knowledge, we are describing the first case of urticaria pigmentosa without pruritus. The patient had a positive Darier's sign, stated that they never felt itchy, and denied ever using a topical steroid or antihistamine. Although our patient declined additional testing, patients like this may benefit from a detailed evaluation of their sensory system through both quantitative sensory testing and genetic analysis.

J Drugs Dermatol. 2024;23(3):e81-82. doi:10.36849/JDD.7558e

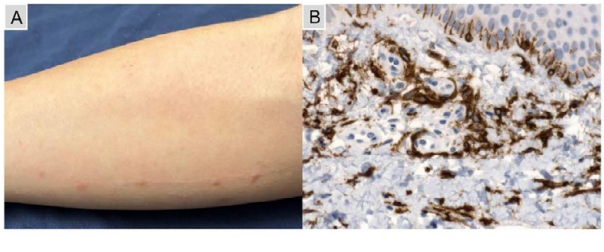
INTRODUCTION

Mastocytosis describes a group of disorders with a pathologic accumulation of mast cells in various tissues. Urticaria pigmentosa is mastocytosis of the skin, which manifests as mastocytomas that can produce hives and pruritus when irritated. To our knowledge, we are reporting the first case of urticaria pigmentosa without any manifestation of pruritus.

CASE REPORT

A 27-year-old female presented to the clinic with reddish-brown macules involving all cutaneous surfaces, excluding the face, palms, and soles. Upon stroking the macules on the patient's forearm, the macules became swollen and erythematous, eliciting a positive Darier's sign (Figure 1A). A physical examination was negative for hepatomegaly and splenomegaly, but the abdomen was mildly tender. Lymphadenopathy was not detected in the groin, axillae, inguinal, or cervical lymph nodes. Muscle strength was full and symmetric with normal tone and symmetric reflexes. Sensory testing, including vibration sense, was normal. Serum tryptase level was 28 ng/mL (RR, 0-11.4 ng/mL). The patient reported having long-standing episodic bouts of diarrhea and headaches. Moreover, the patient stated that she never feels itching and has never used an antihistamine or topical steroid. A biopsy from a lesion on the forearm demonstrated increased mast cell proliferation. Giemsa staining, immunohistochemical stains for CD117 (Figure 1B), and mast cell tryptase showed 30 mast cells in a high-powered field.

FIGURE 1. Urticaria Pigmentosa. (A) Darier's sign after stroking areas with mastocytomas on the right forearm. (B) Histopathological specimen from mastocytoma with immunohistochemistry for CD117 showing numerous mast cells (original magnification x400).



DISCUSSION

Mastocytosis is characterized by the pathologic increase of mast cells in tissues, often associated with mutations in the receptor tyrosine kinase KIT (also termed c-KIT or CD117). Mast cells originate from CD34+ progenitor cells in the bone marrow, and they contain a variety of vasoactive mediators that normally function to protect the body via inflammatory responses.[1] A mutation in the KIT gene or abnormalities in KIT regulation affect the growth, differentiation, and activation of mast cells.[2] In mastocytosis, there is a pathologic activation of the c-*kit* (CD 117) receptor, leading to unregulated clonal expansion and activation of mast cells. Mastocytosis classically presents with pruritus.

doi:10.36849/JDD.7558e

This patient had a positive Darier's sign, headaches, and loose stools. These signs suggest that mast cells were functioning with active histamine release. The congenital lack of pruritus, with the report of never having used an antihistamine or topical steroids, along with normal sensation on examination suggests that the patient may also have issues with neuronal nociception.

Recently, several human channelopathies involving voltage-gated sodium channels (Na_V) have been identified in somatosensory and nociceptive neurons. There are nine Na_V channel family members ($Na_V1.1$-$Na_V1.9$) whose functions are determined by the nine distinct pore-forming alpha-subunits. Of these, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ have been implicated in itch signaling.[3]

Pruritogens can activate G-protein-coupled receptors located on nerve endings of primary sensory neurons resulting in a rise in calcium levels. The subsequent membrane depolarization leads to Na_V opening and transmission of itch. In patients with congenital insensitivity to pain, the $Na_V1.7$ mutation leads to human pain insensitivity and deficits in itch and temperature discrimination.[4] It was found that $Na_V1.8$-/- knock-out models demonstrate impaired histamine and serotonin pruritic scratching.[3] There is evidence that a gain-of-function mutation in $Na_V1.9$ alters sensory information from the periphery to the spine, causing debilitating itch and altered pain signaling.[5] Thus there appears to be a primary role of $Na_V1.7$ and a contributory role of $Na_V1.9$ in pruritic scratching. Time course studies suggest that $Na_V1.8$ is responsible for prolonged pruritus.[3] Mutations leading to such channelopathies, differential signaling expression, and/or altered anatomical expression of $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ could present with a phenotype of nonpruritus.

In such cases as ours, patients should have a detailed evaluation of their sensory system through quantitative sensory testing as well as genetic analysis. Our patient declined to have these.

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.7720e

March 2024 e83 Volume 23 • Issue 3

CASE REPORT

Journal of Drugs in Dermatology

Pemphigus Vulgaris Successfully Treated With Bromocriptine Abstract

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ABSTRACT

Pemphigus vulgaris (PV) is an autoimmune blistering skin condition primarily treated with immunosuppressive agents. We describe a case of PV successfully treated with nonconventional treatment, bromocriptine mesylate. Bromocriptine has been used in human trials showing beneficial therapeutic effects in managing autoimmune conditions. The results from experimental trials and the low toxicity of bromocriptine in comparison with immunosuppressive agents form a solid rationale for investigating its role in controlling PV.

J Drugs Dermatol. 2024;23(3):e83-85. doi:10.36849/JDD.7720e

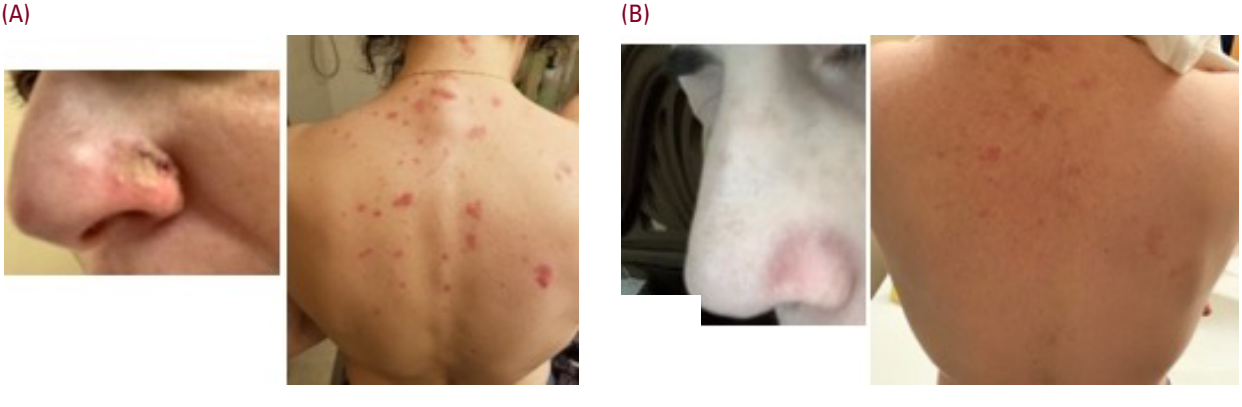
INTRODUCTION

Pemphigus vulgaris (PV) refers to a group of autoimmune, blistering diseases that results in lesions affecting predominantly the mucosa and skin. Autoantibodies (anti-Dsg1 and anti-Dsg3) target desmogleins (Dsg1 and Dsg3), expressed respectively in superficial epidermis and mucosa, and cause loss of cell adhesion.[5] Glucocorticoids are the first-line treatment for pemphigus vulgaris followed by immunosuppressants such as mycophenolate mofetil, methotrexate, or more recently a b-cell- depleting therapy with rituximab, is also well-established. Here, we describe the case of a patient who refused conventional forms of treatment and responded well to a nonconventional treatment (bromocriptine mesylate) in combination with a low dose of prednisone.

CASE REPORT

A 45-year-old female presented in March 2022 with a two-year history of being diagnosed with PV. The patient reported a flare including umbilical involvement, crusted lesions on the scalp and erosions that caused itching and burning sensation on face, trunk, and abdomen (Figure 1A). There was no mucosal involvement noted at the time of flare. The scalp ulcerations caused significant discomfort, affecting patient's ability to sleep. Patient complained of severe itching with subsequent burning over the lesions. Her blood test revealed highly elevated Dsg-1 (131 U/mL) and relatively elevated Dsg-3 (6 U/mL) (Table 1). In November 2020, abdominal punch biopsy was carried out and report revealed intraepidermal acantholytic blister with a supra-basal cleavage plane consistent with the diagnosis of

FIGURE 1. Clinical photographs of pemphigus vulgaris at initial presentation in March 2022 (A) and after bromocriptine treatment in June 2022 (B).



doi:10.36849/JDD.7720e

TABLE 1.

Timeline of Disease Progression and Administration of Treatment Modalities

Dates	Prolactin (ng/mL)	Anti-Dsg1 (u/mL)	Anti-Dsg3 (u/mL)	Symptoms	Treatment (mg/day)
11/05/2020	--	38	103	Flare (external and mucosal)	PD 60
12/01/2020	--	153	124	External and mucosal blisters	PD 60
02/24/2021	--	2	5	External blisters	PD 60
05/26/2021	--	3	4	No symptoms	PD 10
08/10/2021	--	1	1	No symptoms	--
10/20/2021	--	1	0	No symptoms	--
12/21/2021	--	5	1	No symptoms	--
02/04/2022	--	--	--	No symptoms	--
03/17/2022	--	131	6	Flare (external)	--
04/20/2022	9	--	--	External blisters	--
05/12/2022	14.2	--	--	External blisters	PD 40
06/29/2022	--	70	1	No symptoms	PD 4 Bromocriptine 3.2
7/25/2022	<1.0 L	69	<9	No symptoms	PD 4 Bromocriptine 3.2
8/23/2022	<1.0 L	126	<9	No symptoms	PD 4 Bromocriptine 3.2
10/03/2022	<1.0 L	91	<9	No Symptoms	PD 4 Bromocriptine 3.2
11/15/2022	<1.0 L	56	<9	No Symptoms	PD 4 Bromocriptine 3.2
12/22/2022	--	76	4	No Symptoms	PD 2 Bromocriptine 3.2
03/06/2023	--	186	9	No Symptoms	PD 2 Bromocriptine 3.2

PV. The blood test revealed relatively elevated Dsg-1 (38 U/mL) and highly elevated Dsg-3 (103 U/mL) (Table 1). Considering all the clinical features, histopathological findings, and results of immunological PV was diagnosed and treatment with prednisolone (60 mg/day) was started. It should be noted that the patient had made considerable changes to her diet, excluding sugar products and bread, and limiting carbohydrates intake to certain fruits. Prednisone treatment resulted in complete remission in 4 months and the patient started tapering prednisone starting in March 2021 reaching a stable dose of 10 mg/day. The patient remained blister-free and off prednisone from June 2021 until March 2022 (Table 1).

To address the flare-up, the patient was prescribed prednisone at a dose of 40 mg/day at the beginning of May 2022 and refused any adjunct immunosuppressant agents. The prednisone dose was sufficient to control the disease and led to slow healing of the skin lesions within 2 weeks following prednisone intake. Since the patient was against the use of immunosuppressant agents and started tapering off prednisone, the patient was prescribed bromocriptine mesylate (Cycloset, Santarus, Inc) as adjunct treatment at a daily dose of 0.2 mg taken in the morning 2 hours after waking up, followed by food intake (regimen protocol suggested by McMurray for autoimmune patients.)[1]

The patient noted significant improvement in the healing rate of ulcers and hyperpigmentation (Figure 1B). Bromocriptine dose was stepped up gradually at the rate of 0.2 mg/day, as the patient tapered prednisone at an approximate rate of 1 mg every day. Despite rapid tapering of prednisone, and elevated Dsg-1 levels, the patient's condition remained stable, as bromocriptine was stepped up 0.2 mg/daily reaching 3.2 mg. By the end of June 2022, prednisone at a dose of 2 mg and bromocriptine at a dose of 3.2 mg remained the only treatment options. The patient took 3 pills (2.4 mg) in the morning upon waking up, the last pill (0.8 mg) was taken before bedtime. The patient remained symptom free upon then.

DISCUSSION

The literature describes experimental studies with the use of bromocriptine mesylate in individuals with autoimmune conditions.[2] Its use has been observed in human trials primarily with systemic lupus patients. The rationale for treating autoimmune diseases with bromocriptine has been drawn from the observation that prolactin (PRL) acts as a cytokine.[2,3] Bromocriptine stimulates dopamine receptors suppressing pituitary secretion of PRL and immune responses. The relationship between PRL and the immune system has been demonstrated in the last two decades, opening new windows in the field of immune endocrinology. The immunomodulatory effect of PRL on immune responses in association with PV has been examined by Lajevardi et al (2016).[4] The results of this cross-sectional study show that PV female patients were substantially more likely to have relatively higher prolactin levels. Given the

doi:10.36849/JDD.7720e

suppressive effect of bromocriptine on the pituitary production of prolactin, bromocriptine has been prescribed to autoimmune patients as an adjunctive therapy allowing to maintain a low dose of prednisone as the main treatment.[1] While the depression of PRL production has served as a possible explanation of bromocriptine use in autoimmune conditions, an additional potential mechanism associated with the use of bromocriptine mesylate may be explained through its sympatholytic dopamine effect.[5] The literature is replete with studies supporting that chronic elevation of sympathetic tone leads to increased cellular oxidative stress and inflammation.[6,7] Higher cellular oxidative stress and inflammatory state in multiple tissues are also associated with low central dopaminergic activity.8 Timed administration of bromocriptine within 2 hours of awakening leads to an increase in low hypothalamic dopamine levels and inhibition of sympathetic tone within the central nervous system, resulting in lower cellular oxidative stress.[5] At the same time, oxidative stress has been proposed as a contributory mechanism of autoimmune skin conditions, including PV.[9] Given these associations, the beneficial therapeutic effect of bromocriptine in human trials and its low toxicity compared to conventional treatment modalities, further research is needed to examine its mechanism and potential in controlling PV.

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.7603

March 2024 e86 Volume 23 • Issue 2

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Examining the Uncertainties Surrounding Exosome Therapy in Androgenetic Alopecia: A Call for Evidence-Based Practice

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ABSTRACT

Hair loss, a pervasive and often distressing condition, affects a substantial number of individuals globally. Although conventional treatments such as hair transplantation, topicals, oral medications, and injectables exist, they have limitations, including the necessity for repeated treatments, potential adverse effects, and cost barriers. Exosome therapy, an innovative and burgeoning option within regenerative medicine, offers a novel approach to hair loss treatment. Exosomes are small vesicles that are produced from the membranes of late-endosomes and secreted by cells, playing a crucial role in intercellular communication. Research on humans is limited,[1-4] and animal studies have shown that exosomes derived from various cell types can stimulate hair growth, resulting in increased research and development of exosome therapy for hair loss.[5] Establishing a uniform reporting method for exosome therapy is vital as research in this area continues to expand. A standardized approach to research reporting and results is essential for comprehending the underlying mechanisms, safety, and efficacy of exosome therapy. This article provides an in-depth analysis of the current state of exosome therapy for hair loss, including potential advantages, and limitations, as well as directions for future research.

J Drugs Dermatol. 2024;23(3):e86-90. doi:10.36849/JDD.7603

INTRODUCTION

Understanding Exosome Therapy

Exosome therapy represents a cutting-edge approach in regenerative medicine, leveraging the potential of exosomes derived from optimal cellular environments to achieve specific therapeutic effects in target areas. In the context of hair loss, the objective is to stimulate hair growth by harnessing exosomes carrying signaling molecules or genetic material known to promote hair follicle development, growth, and maintenance.[6]

To commence exosome therapy, the desired exosomes are isolated from a tissue source expressing high levels of target signaling molecules. Tissue sources can include human tissues such as adipose tissue, bone marrow, placenta, umbilical cord, and foreskin, or animal tissues such as porcine or murine adipose tissue, bone marrow, or bovine milk. The choice of tissue source depends on the target signaling molecules, desired therapeutic application, as well as ethical, safety, and regulatory considerations.

Following the selection of an appropriate tissue source, the tissue is processed to extract the target exosomes with optimum quality and purity ensured. This step involves the utilization of quantification and qualification methods, including but not limited to electron microscopy, reverse transcription-polymerase chain reaction, and western blotting. Careful selection of tissue sources and stringent quality control measures during exosome extraction enable researchers to develop more effective and targeted exosome therapies for various medical conditions, including hair loss.

Exosome therapy for hair regrowth is based on the principle that exosomes derived from optimal cellular environments can induce specific effects on hair follicles. Upon being introduced into the scalp, exosomes containing signaling molecules or genetic material associated with hair growth are transferred to hair follicle cells, promoting hair growth by encouraging cell proliferation, differentiation, and survival.[2]

Exosomes utilized for hair regrowth may contain various signaling molecules involved in hair follicle development, growth, and maintenance. These can include growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF-1), and keratinocyte growth factor (KGF), as well as signaling pathways like wingless-related integration site (Wnt) /β-catenin, Sonic hedgehog (Shh), and bone morphogenetic protein (BMP).[3] When introduced into the scalp, these signaling molecules

doi:10.36849/JDD.7603

are transferred to hair follicle cells, stimulating hair growth by promoting cell proliferation, differentiation, and survival.

Moreover, growth factors such as IGF-1, KGF, and VEGF can enhance hair growth by improving blood flow to hair follicles and supplying essential nutrients and oxygen.[4] These factors can also stimulate the production of extracellular matrix components, offering structural support to hair follicles and maintaining their integrity.

In conclusion, exosome therapy holds significant potential for hair loss treatment, offering a novel and innovative solution to a prevalent and distressing condition. The advancement of exosome therapy hinges on further research to elucidate its mechanisms of action, long-term effects, and the development of a standardized approach for reporting study results.

Quality of Studies on Exosome Therapy for Hair Loss

While numerous studies have explored the potential benefits of exosome therapy for hair loss in mice, and a few in vitro studies on human hair dermal papilla cells and hair follicles have been conducted, there are currently minimal published human studies.[1-3] One study utilizing exosomes in human subjects has recently commenced in Isfahan, Iran; however, the current evidence supporting the use of exosome therapy for hair loss remains limited.[7] Given the lack of human studies, it is crucial to exercise caution in interpreting results from animal studies and in vitro studies, as they may not always be directly translatable to humans. Additionally, the methodologies used in these studies vary greatly, making it challenging to compare results and draw conclusions regarding the overall efficacy of exosome therapy for hair loss.

It is essential to address the claims made by some practitioners about the long-lasting effects of a single or limited treatment with exosome therapy. To date, these claims have not been substantiated by research. Long-term studies are necessary to determine the maintenance of treatment effects, and the scientific community should emphasize the importance of such research.

This underscores the importance of standardizing research methodologies and conducting well-designed clinical trials to establish the safety and efficacy of exosome therapy for hair loss in humans. Until more robust evidence is available, it is likely premature to recommend exosome therapy for hair loss to patients. Further research is necessary to determine the optimal dosing, duration of treatment, and safety profile of exosome therapy for hair loss.

Standardization of Exosome Therapy Production and Reporting

Standardization is critical for ensuring the safe and effective use of exosome therapy. The process of obtaining exosomes can vary significantly depending on the source. Autologous exosomes, taken from and given to the same patient, may not require the same level of processing as allogenic exosomes, which are pre-made and ready to use. Pre-made exosome kits, marketed as exosome therapy, can raise concerns due to their often lacking transparency regarding the source and contents of the exosomes. The limited disclosure of the exact contents and potential side effects of these exosomes could pose a significant risk to patients and may lead to life-threatening responses.[2] For these reasons, the use of exosome therapy products outside of federally registered clinical trials is currently illegal in the United States. It is essential for clinicians to understand the contents and effects of exosomes before administering them to patients.

Efforts have been made to standardize exosome therapy production and administration. In 2014, the International Society for Extracellular Vesicles (ISEV) proposed Minimal Information for Studies of Extracellular Vesicles ("MISEV") guidelines, which were further updated in 2018. These contained recommendations on the most appropriate methods of extracellular vesicle isolation, characterization, and reporting. The National Institute of Standards and Technology (NIST) developed reference materials to be used for extracellular vesicle development and reporting. We propose standardized reporting guidelines to be used for exosome therapy research (Table 1) that can help accelerate the translation of exosome-based therapies from laboratories to the clinic.[8,9]

Exosome Signaling Molecules for Hair Loss

Despite FDA regulations on the use of exosomes in human subjects, research into their use for hair loss continues. In hair loss research, exosomes often contain signaling molecules involved in promoting hair growth, such as β-catenin, Norrin, Fzd4, Shh, IGF-1, KGF, HGF, Wnt, BMP, miR-22-5p, miR-218-5p, and others (Table 2).[10] Autologously derived exosomes are frequently injected into the scalps of laboratory rodents, where they can deliver growth factors and other therapeutic molecules to hair follicles, demonstrating promising results in stimulating new hair growth.

Importance of Creating a Uniform Reporting Method for Exosome Therapy

As research on the potential use of exosome therapy expands, it is crucial to establish a uniform reporting method for research in this area. A standardized approach to reporting research results and patient outcomes will provide a more comprehensive and accurate understanding of the benefits and limitations of exosome therapy, as well as facilitate the development of evidence-based guidelines for treating hair loss with exosome therapy. A uniform reporting method will also promote transparency and consistency in the field, enabling accurate comparison of results across different studies. This will help identify and address any disparities in research quality

doi:10.36849/JDD.7603

TABLE 1.

Standardized Reporting Guidelines	
Section	**Guidelines**
Study Design and Population	1. rovide detailed information on the study design (control groups, blinding, randomization) 2. Specify target population (age, sex, ethnicit 3. Define type and stage of hair lo 4. eport sample size and rationale
Exosome Source and Isolation	5. Describe source of osomes and type of donor cells 6.Detail isolation methods and protocols 7. State haracterization methods used to confirm exosome presence and purity
Exosome Characterization and QC	8. eport presence and relative abundance of key signaling molecules 9. Describe quality control measures to ensure consistency and poten
Intervention and Administration	10. Specify route of administration and frequency/duration of treatme 11. Describe dose of e osomes and rationale for selection 12. Detail co-treatments or adjunct therapi
Outcome Measures and Evaluation	13. Define primary and secondary outcome measur 14. Detail methods and instruments used to assess outcom 15. Specify time points for assessments and rationa
Safety and Adverse Events	16. eport observed adverse events or side effects (severity, duration, relationship to therapy) 17. Describe safety monitoring procedures and risk miti ation strategies
Statistical Analysis	18. Detail statistical methods used to anal e data, including subgroup/sensitivity analyses 19. eport effect sizes, confidence intervals, and *P*-values for all outcome measures
Results and Interpretation	20. resent results clearly using tables, figures, or graphs 21. Discuss findings in context of existing literature and study limitation 22. Address potential biases or confounding factors
Transparency and Data Sharing	23. Encourage open access to the study protocol, data, and relevant materi 24. Consider registering the study in a public registry or repository for data sharing and collaborat

QC: Quality Control

TABLE 2.

Key Signaling Molecules and Their Roles in Hair Follicle Development and Growth	
Signaling Molecule	**Role in Hair Growth**
β-catenin	Involved in the Wnt signaling pathway, which plays a crucial role in hair follicle development and cycling. It is required for the initiation of hair follicle growth and the maintenance of hair follicle stem cells.
Norrin	A secreted protein that binds to Fzd4 and activates the Wnt/β-catenin signaling pathway, promoting hair follicle morphogenesis, growth, and maintenance.
Fzd4	A receptor for Norrin and Wnt ligands, involved in the activation of the Wnt/β-catenin signaling pathway, which is essential for hair follicle development and cycling.
Shh (Sonic Hedgehog)	A morphogen involved in hair follicle development and the regulation of hair follicle growth. It stimulates the proliferation and differentiation of hair follicle cells and promotes the anagen phase of the hair cycle.
IGF-1 (Insulin-like Growth Factor 1)	Stimulates hair follicle growth by promoting cell proliferation, differentiation, and migration in hair follicles. It also extends the anagen phase of the hair cycle and enhances the hair shaft diameter.
KGF (Keratinocyte Growth Factor)	Stimulates the growth and differentiation of keratinocytes, which are critical for hair follicle structure and function. It promotes hair growth by prolonging the anagen phase and improving the hair shaft diameter.
HGF (Hepatocyte Growth Factor)	Promotes hair follicle growth by stimulating the proliferation and differentiation of hair follicle cells. It also acts as a mitogen for hair follicle dermal papilla cells and contributes to the hair cycle progression.
Wnt	A family of secreted proteins that play a crucial role in hair follicle development and cycling through the activation of the Wnt/β-catenin signaling pathway. They regulate hair follicle stem cell maintenance, proliferation, and differentiation.
BMP (Bone Morphogenetic Protein)	Regulates hair follicle development, cycling, and stem cell maintenance. BMP signaling inhibits hair follicle growth, and its suppression is required for the anagen phase initiation and maintenance.
miR-22-5p	A microRNA that modulates gene expression in hair follicle cells. It promotes hair growth by targeting and suppressing negative regulators of the Wnt/β-catenin and BMP signaling pathways, which are critical for hair follicle development and cycling.

doi:10.36849/JDD.7603

DISCLOSURES

Dr Shapiro is a consultant for Pfizer, Eli Lilly, Eirion, Follica, and Replicel Life Sciences. Drs Shapiro and Lo Sicco have been investigators for Regen Lab and are investigators for Pfizer. Dr Lo Sicco is a consultant for Pfizer and Aquis. MGB, LA, and MI have no conflicts to disclose.

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doi:10.36849/JDD.7653e

March 2024 e91 Volume 23 • Issue 3

LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Efficacy of Low-Dose Spironolactone for Hair Loss in Women

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INTRODUCTION

Female pattern hair loss (FPHL) results from a combination of hormones, aging, and genetics, and is the most common type of alopecia in women. Topical minoxidil remains the only United States Food and Drug Administration (FDA)-approved treatment for this condition, although numerous other therapies have demonstrated efficacy in recent years.[1] Spironolactone, an androgen receptor inhibitor, and potassium-sparing diuretic has largely been thought to be effective for FPHL only at higher doses of >100-200 mg daily.[2] The efficacy of low-dose spironolactone of <50 mg daily is particularly underexplored and may be beneficial in patients who are unable to tolerate higher doses of spironolactone, or in older patients who are at higher risk of hyperkalemia.

A retrospective chart review was conducted on adult women at a specialty alopecia clinic with FPHL treated with low-dose spironolactone, defined as ≤50 mg daily, either as monotherapy or combination therapy with other therapeutic agents. Data on age, diagnosis, duration of hair loss, race, and concomitant medications were collected (Table 1). FPHL severity was measured using the Sinclair Scale (grade 1-5; Table 2).

We identified 62 patients with FPHL seen in the clinic from June to December 2022 treated with low-dose spironolactone. Among them, 30 (48.39%) patients were diagnosed with FPHL, and 32 (51.61%) patients were diagnosed with FPHL and concomitant scarring alopecia, namely frontal fibrosing alopecia (FFA) or lichen planopilaris (LPP). The average age was 62 years (range 30–84) and the average duration of hair loss was 4.84 years (range 1 to 34). Amongst all patients, 54 (87.1%) identified as Caucasian, 5 (8.1%) as Asian, 2 (3.2%) as Black, and 1 (1.6%) as Hispanic. Spironolactone's daily dose ranged from 12.5 mg to 50 mg, with an average dose of 35.28 mg. The average Sinclair scale before starting spironolactone and approximately 1 year after starting low-dose spironolactone decreased significantly from 2.47 to 1.81 (P=<0.001). The decrease in Sinclair scale remained significant when stratified by diagnosis.

Most patients were on concomitant medications and therapeutics, namely topical minoxidil 5% foam and/or low-level light laser treatment for at least 1 year before starting spironolactone. Twenty-eight (45.16%) patients were taking low-dose oral minoxidil (dose range 0.625–5 mg) for an average of four months (range 0 to 18 months). Fourteen (22.58%) patients were treated with platelet-rich plasma injections. Excluding these 42 patients from the analysis, a statistically significant difference in average Sinclair Score remained pre-and post-treatment, decreasing from 2.63 to 1.95 (P=0.004).

Reported adverse events included polyuria in 3 (4.8%) patients, lightheadedness in 3 (4.8%) patients, spotting in 2 (3.2%) patients, headaches in 1 (1.6%) patient, and hyponatremia (1.6%) in 1 patient. Mild hyperkalemia (K=5.0-5.1) was detected in 3 (4.8%) patients. All side effects resolved upon dose reduction except for polyuria in 1 patient. These side effects were mild and did not lead to discontinuation of the medication in any patients.

Low-dose spironolactone may be an effective treatment for FPHL, especially for patients who are unable to tolerate higher doses, or for patients at higher risk of side effects. Our study is limited by its retrospective nature and small sample size. Removal of those treated with multiple FPHL medications, including patients with concomitant scarring alopecia, however, still demonstrated a reduction in FPHL severity, which strengthens these findings. Further large-scale studies may be helpful to better understand the efficacy and tolerability of spironolactone in this population.

doi:10.36849/JDD.7653e

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TABLE 1.

Demographics and Characteristics of Patients Treated With Low-Dose Spironolactone		
Characteristics	**Patients with FPHL (n=62)**	
Age (years)	61.56 ± 13.40 (range 30-84)	
Length of Diagnosis (years)	4.84 ± 6.88 (range 1-34)	
Dose (mg)	35.28 ± 14.23 (range 12.5-50)	
Race		
Caucasian	54 (87.10%)	
Asian	5 (8.06%)	
Black	2 (3.22%)	
Hispanic	1 (1.60%)	
Diagnosis		
FPHL	30 (48.39%)	
FPHL + Scarring Alopecia	32 (51.61%)	
Recent Other FPHL Treatments		
Oral Low-Dose Minoxidil	28 (45.61%)	
Platelet-Rich Plasma Injections	14 (22.58%)	
Adverse Effects	**# (%) of Patients**	**# (%) Resolved with Dose Change**
Hyperkalemia (K=5.0-5.5)	3 (4.84%)	3/3 (100%)
Hyponatremia (Na=130-134)	1 (1.61%)	1/1 (100%)
Polyuria	3 (4.84%)	2/3 (66.7%)
Spotting	2 (3.22%)	2/2 (100%)
Breast Tenderness	0 (0%)	--
Dizziness/Lightheadedness	3 (4.84%)	3/3 (100%)
Headache	1 (1.61%)	1/1 (100%)

TABLE 2.

Changes in Sinclair Scale From Baseline to 1 Year			
Characteristics	**Sinclair Scale Baseline**	**Sinclair Scale 1-Year**	***P*-value**
All Patients (n=62)	2.47 ± 0.85	1.81 ± 0.72	0.000*
FPHL Only (n=30)	2.43 ± 0.85	1.82 ± 0.69	0.002*
FPHL + Scarring Alopecia (n=32)	2.52 ± 0.87	1.80 ± 0.77	0.000*
Spironolactone "Monotherapy" (n=20)	2.63 ± 0.89	1.95 ± 0.81	0.004*

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.7738e

March 2024 e93 Volume 23 • Issue 3

LETTERS TO THE EDITOR

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Complementary and Alternative Medicine for Hidradenitis Suppurativa Discussed on TikTok: A Cross-Sectional Analysis

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a painful, chronic inflammatory skin disease that negatively affects patient quality of life, and conventional treatments are variably effective. As a result, patients often turn to complementary and alternative medicine (CAM) for pain relief. Social media enables HS patients to share treatment recommendations. TikTok is a popular social media platform, but little is known about the HS treatments discussed in TikTok videos.

Objective: To evaluate the content and quality of information on TikTok regarding CAM HS therapies.

Methods: A cross-sectional analysis was conducted by performing a search in TikTok using the terms #hidradenitissuppurativa, #hswarrior, #naturalremedy, #complementarymedicine, #alternativemedicine, and #HStreatment. Two independent reviewers evaluated video quality using the DISCERN and AVA instruments. Linear regressions compared the engagement, DISCERN, and AVA scores among different uploader types.

Results: In total, 91 TikTok videos were analyzed. Videos were uploaded by non-physicians (82.4), dermatologists (6.6%), and private companies (11.0%). The average DISCERN and AVA scores were 36.2 and 1.6, respectively (poor quality). Common CAM therapies were natural salves, turmeric, Epsom salts, elimination diets, and zinc supplements. Physician-uploaded videos were of significantly higher quality than videos by other uploader types, with an average DISCERN and AVA score of 44.3 ($P<0.009$) and 2.6 ($P<0.001$), respectively (fair quality).

Conclusion: TikTok videos were poor quality (low DISCERN and AVA scores); physician-uploaded videos were fair quality. Dermatologists can improve video quality by adequately discussing the supporting evidence, mechanisms of action, and remaining questions for HS treatments.

J Drugs Dermatol. 2024;23(3):e93-96. doi:10.36849/JDD.7738e

INTRODUCTION

Hidradenitis suppurativa (HS) is a painful, chronic inflammatory skin disease that negatively impacts quality of life.[1-6] Conventional HS therapies are variably effective,[2] and patients often turn to complementary and alternative medicine (CAM) for relief.[6]

Most evidence supporting CAM therapies is anecdotal.[3] Social media enables HS patients to share treatment recommendations with one another.[1,7-10] TikTok is a popular social media platform, but little is known about the HS treatments discussed in TikTok videos.[11] This study aims to evaluate the content and quality of information shared on TikTok regarding CAM therapies for HS to better understand patient experiences and facilitate physician-patient discussions.

MATERIALS AND METHODS

A cross-sectional analysis was conducted by performing a search in TikTok using the terms #hidradenitissuppurativa, #hswarrior, #naturalremedy, #complementarymedicine, #alternativemedicine, and #HStreatment. The top 60 videos discussing CAM HS treatments and the top 31 videos discussing conventional HS treatments were included. Videos were analyzed if they discussed HS treatment, and if they contained audio and/or text that could be analyzed for content quality. Videos were excluded if they did not meet these requirements.

For each video, descriptive characteristics, including uploader type (physician, non-physician, or private company) and viewer engagement score were collected.

doi:10.36849/JDD.7738e

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TABLE 1.

Descriptive Characteristics of TikTok Videos Discussing HS Treatment Options

	No. of Videos (%)	Mean No. of Likes	Mean No. of Comments	Mean No. of Views	Mean No. of Favorites	Mean Engagement Score (SEM)	Mean Discern Score (SEM)	Mean AVA Score (SEM)
Uploader Type								
Non-physician	75 (82.4)	2502.7	68.4	92,190.8	285.7	0.03 (0.003)	35.9 (0.8)	1.6 (0.1)
Physician	6 (6.6)	47764.0	635.2	1,117,700.0	9188.7	0.03 (0.01)	44.3 (2.9)	2.6 (0.2)
Private Company	10 (11.0)	357.5	18.7	20,475.5	71.3	0.02 (0.01)	33.1 (3.6)	1.4 (0.3)
Gender								
Female	78 (85.7)	4793.5	85.6	138085.0	696.0	0.03 (0.002)	35.6 (0.8)	1.6 (0.1)
Male	8 (8.8)	12169.9	300.4	352562.5	2795.6	0.04 (0.01)	40.8 (3.1)	2.3 (0.3)
N/A or Unknown	5 (5.5)	1647.0	13.5	58123.0	413.0	0.03 (0.01)	40.6 (7.9)	1.8 (0.6)
Video Category								
Information/how-to	18 (19.8)	16662.3	231.8	401741.2	3405.4	0.03 (0.004)	40.9 (2.0)	2.1 (0.2)
Information/how-to and personal anecdote	7 (7.7)	1183.1	38.9	37736.6	257.7	0.03 (0.01)	37.6 (2.6)	1.7 (0.2)
Information/how-to and product advertisement	2 (2.2)	173.5	3.0	30314.0	4.0	0.01 (0.01)	34.5 (6.0)	1.5 (0.5)
Personal anecdote	49 (53.9)	3222.4	87.3	115666.2	307.6	0.03 (0.003)	35.5 (1.1)	1.6 (0.1)
Personal anecdote and product advertisement	6 (6.6)	415.0	19.5	21038.3	75.7	0.03 (0.01)	35.1 (2.0)	1.3 (0.2)
Product advertisement	9 (9.9)	991.4	31.8	52807.0	187.7	0.02 (0.002)	30.1 (1.6)	0.9 (0.2)

HS, hidradenitis suppurativa; SEM, standard error of the mean; AVA, Armstrong Viewer Assessment

Two independent reviewers evaluated video quality using the Armstrong Viewer Assessment (AVA) and the validated DISCERN instrument.[12,13] Possible DISCERN scores range from 16-26 (very poor), 27-38 (poor), 39-50 (fair), 51-62 (good), and 63-75 (excellent).[12] AVA scores range from 0 (very poor) to 4 (very good).[13]

Linear regressions were conducted to compare engagement, DISCERN, and AVA scores among different uploader types. Three linear regressions were performed to compare one uploader type to the other uploader types combined (eg, physician-uploaded videos were compared to videos uploaded by non-physicians and private companies combined).

RESULTS

Overall, 91 TikTok videos were analyzed. Most videos (82.4%) were uploaded by non-physicians, 6.6% by dermatologists, and 11.0% by private companies (Table 1). The average DISCERN and AVA scores were 36.2 and 1.6, respectively (poor quality). Lower scores signify worse quality, while higher scores signify better quality. The most mentioned HS treatments and CAM therapies are listed in Tables 2 and 3, respectively. Common CAM therapies were natural salves, turmeric, Epsom salts, elimination diets, and zinc supplements (Table 3).

Compared to videos uploaded by physicians and private companies, non-physician videos did not differ in viewer engagement (P=0.548) or quality (DISCERN score: P=0.547, AVA score: P=0.293; Table 4). Compared to videos uploaded by non-physicians and private companies, physician-uploaded videos did not differ in viewer engagement (P=0.550); video quality was significantly higher with an average DISCERN and AVA score of 44.3 (P<0.009) and 2.6 (P<0.001), respectively (fair quality) (Tables 1, 5). Compared to physicians and non-physicians, private company videos did not differ in viewer engagement (P=0.227) or quality (DISCERN score: P=0.193, AVA score: P=0.211; Table 6).

TABLE 2.

Most Common Treatments for HS Mentioned in TikTok Videos Overall

Treatment Type	% of Videos Mentioned
CAM skincare recommendations	34.1%
Dietary changes	25.3%
Hibiclens solution	18.7%
Topical antibiotics	15.4%
Biologic medications	12.1%
Vitamins, supplements	11.0%
Advice on wound care	11.0%
Oral antibiotics	9.9%
Epsom salt baths	7.7%
Topical benzoyl peroxide	5.5%
Surgery	5.5%
Topical analgesics	5.5%

HS, hidradenitis suppurativa; CAM, complementary and alternative medicine

doi:10.36849/JDD.7738e

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TABLE 3.

Most Common Specific CAM Treatments for HS Mentioned in TikTok Videos	
Treatment Type	% of Videos Mentioned
Beeswax and propolis salve	9.9%
Turmeric	8.8%
Epsom salt baths	7.7%
Autoimmune elimination protocol diet	6.6%
Zinc supplements	4.4%
Apple cider vinegar	3.3%
Exfoliation	3.3%
Tea tree oil	3.3%
Vitamin E oil	3.3%
Topical products with unknown ingredients	3.3%
Castile soap	3.3%

CAM, complementary and alternative medicine; HS, hidradenitis suppurativa

DISCUSSION

HS is a painful, chronic disease, and patients often turn to CAM therapies for relief.[5] This study is among the first to investigate CAM HS treatments discussed on TikTok. The most common CAM HS treatments included beeswax and propolis salves, turmeric, Epsom salt baths, elimination diets, and zinc supplements.

While these CAM therapies lack strong evidence supporting their efficacy for treating HS, they may have therapeutic benefits.[14-17] For example, propolis and beeswax possess anti-inflammatory and antimicrobial properties.[15] Magnesium in Epsom salts may regulate keratinocyte proliferation, and zinc has been found to promote wound healing in cases of mild-moderate HS.[14,18] Turmeric possesses anti-inflammatory and immune-regulatory effects.[16,17] Elimination diets may balance

TABLE 4.

Linear Regression Comparing Viewer Engagement and Quality of Videos Posted by Non-Physicians Compared to Physicians and Private Companies			
		b-Coefficient (95% CI)	*P*-value*
Engagement Score	Physicians and Private Companies Non-physicians	(Ref) 0.003 (-0.008-0.015)	-- 0.548
DISCERN score	Physicians and Private Companies Non-physicians	(Ref) -1.3 (-5.7 – 3.0)	-- 0.547
Armstrong Viewer Assessment Score	Physicians and Private Companies Non-physicians	(Ref) -0.2 (-0.6 – 0.2)	-- 0.293

*Statistical significance was determined at $P<0.05$.

TABLE 5.

Linear Regression Comparing Viewer Engagement and Quality of Videos Posted by Physicians Compared to Non-Physicians and Private Companies			
		b-Coefficient (95% CI)	*P*-value*
Engagement Score	Non-physicians and Private Companies Physicians	(Ref) 0.005 (-0.012 – 0.023)	-- 0.550
DISCERN score	Non-physicians and Private Companies Physicians	(Ref) 8.7 (2.2 – 15.1)	-- 0.009
Armstrong Viewer Assessment Score	Non-physicians and Private Companies Physicians	(Ref) 1.02 (0.42 – 1.62)	-- 0.001

*Statistical significance was determined at $P<0.05$.

TABLE 6.

Linear Regression Comparing Viewer Engagement and Quality of Videos Posted by Private Companies Compared to Physicians and Non-Physicians			
		b-Coefficient (95% CI)	*P*-value*
Engagement Score	Physicians and non-physicians Private Companies	(Ref) -0.01 (-0.02 – 0.01)	-- 0.227
DISCERN score	Physicians and non-physicians Private Companies	(Ref) -3.5 (-8.8 – 1.8)	-- 0.193
Armstrong Viewer Assessment Score	Physicians and non-physicians Private Companies	(Ref) -0.3 (-0.8 – 0.2)	-- 0.211

*Statistical significance was determined at $P<0.05$.

doi:10.36849/JDD.7738e

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the gut microbiome and decrease inflammation by removing dietary triggers.[17]

Overall, theTikTok videos were poor in quality (low DISCERN and AVA scores); videos did not explain the treatment mechanism of action, risks associated with treatment, supporting evidence, or treatment alternatives. While physician-uploaded videos were significantly higher quality than other uploader types, their average quality was only fair because they did not consistently discuss how treatments worked, provide supporting evidence, or refer to remaining gaps in knowledge. Because most video uploaders were non-physicians, great potential exists for dermatologists to use TikTok to discuss HS.[11] They can utilize this opportunity well by creating videos that adequately discuss the supporting evidence, mechanisms of action, and remaining questions for HS treatments.

DISCLOSURES

Authors HP, PK, KL, DY, MYH, EK, and RA have no conflicts of interest to declare. AWA has served as a research investigator, scientific advisor, or speaker to AbbVie, Amgen, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho, Sun, Dermavant, Dermira, Sanofi, Takeda, Organon, Regeneron, Pfizer and Ventyx." No other changes are required to the other authors' disclosures.

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doi:10.36849/JDD.7949e

March 2024 e97 Volume 23 • Issue 3

LETTERS TO THE EDITOR

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Comparing Clinical Outcomes of Steroid-Sparing Therapy With Rituximab Versus Rituximab Alone in Pemphigus

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ABSTRACT

Background: Previous clinical trials have demonstrated that rituximab therapy combined with conventional steroid-sparing therapy (SST) has increased rates of disease control for mucous membrane pemphigoid compared with rituximab alone. However, limited data is available regarding the role of SST with rituximab therapy in pemphigus.

Objective: This study aimed to examine clinical outcomes in pemphigus patients treated with rituximab with SST versus without the addition of SST.

Methods: A retrospective chart review was performed for adult pemphigus patients in the Southeastern US at Emory between January 1, 2011, and December 31, 2021. Primary outcomes, including time to remission, time to prednisone dose of 10 mg or less, time to cessation of prednisone therapy, and time to relapse after a rituximab cycle, were compared between patients on SST and patients without SST.

Results: Following rituximab therapy, there was no difference in time to remission, time to prednisone dose of 10 mg or less, time to cessation of prednisone therapy, or time to relapse for patients with or without SST.

Limitations: Our study is limited by its retrospective decline, setting at a single academic center, and inclusion of a high proportion of patients with moderate disease.

Conclusions: The use of SST with rituximab dosing did not improve clinical outcomes related to time to remission, reduction in prednisone dosing, or relapse. These data provide further evidence for the use of rituximab in the majority of pemphigus patients without the need for SST.

J Drugs Dermatol. 2024;23(3):e97-99. doi:10.36849/JDD.7949e

INTRODUCTION

Pemphigus is a rare autoimmune blistering disease that is associated with significant morbidity and mortality. Rituximab demonstrated superiority over oral steroid monotherapy and steroid-sparing agent mycophenolate in prior clinical trials and is FDA-approved as first-line therapy for pemphigus.[1,2] Despite improved efficacy, rates of relapse remain high with estimates of 40-50%.[3] While the use of rituximab therapy with conventional steroid-sparing therapy (SST) in patients with mucous membrane pemphigoid showed improved disease control, limited data are available regarding the role of SST as an adjunct to rituximab therapy in pemphigus.[4] A small retrospective study demonstrated decreased relapse rates when severe pemphigus patients were maintained on low-dose SST following rituximab.[5] However, it is unclear whether SST following rituximab offers better outcomes for non-severe pemphigus patients, particularly given the added risk of adverse effects such as infection. Here, we examined a larger, more diverse cohort of pemphigus patients to determine the difference in clinical outcomes including time to remission, relapse, tapering to minimal therapy of prednisone, and adverse events for patients on or off SST at the time of rituximab dosing.

MATERIALS AND METHODS

A retrospective analysis was performed for adult pemphigus patients treated with rituximab at the Emory Clinic between October 2011 and December 2021. Patients included in the analysis had clinically, histologically, and/or serologically confirmed pemphigus. Pemphigus Disease Area Index (PDAI) scores and endpoints were determined by the same provider (RJF) at the time of the visit. Remission (including partial and complete remission) and relapse (3 or more new lesions a month without resolution within one week) were defined by consensus statement.[6] Data are presented as mean (SD) and differences in observed variables were assessed using one-way ANOVA and Fisher's exact tests for numerical and categorical covariates, respectively. A P-value ≤ 0.05 was considered statistically

doi:10.36849/JDD.7949e

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TABLE 1.

Descriptive Statistics and Clinical Characteristics			
	Steroid-sparing therapy* N=37	No steroid-sparing therapy N=82	*P*
Age (mean ± SD)	53.3 ± 16.2	52.1 ± 15.5	0.710
Gender (#, %)	--	--	0.842
Male	14 (37.8)	33 (40.2)	--
Female	23 (62.2)	49 (59.8)	--
Race (#, %)	--	--	0.655
White	15 (40.6)	35 (42.7)	--
Black	14 (37.8)	26 (31.7)	--
Asian	6 (16.2)	11 (13.4)	--
Other (Hispanic, Middle Eastern)	2 (5.4)	10 (12.2)	--
Pemphigus subtype (#, %)	--	--	0.268
Pemphigus vulgaris	25 (67.6)	63 (76.8)	--
Pemphigus foliaceous	12 (32.4)	17 (20.7)	--
Other pemphigus†	0 (0)	2 (2.5)	--
Disease duration, years (mean ± SD)	6.3 ± 8.8	2.8 ± 4.5	0.006
Prednisone dose at time of infusion, mg (mean ± SD)	19.3 ± 12.8	24.0 ± 17.9	0.237
Pre-rituximab PDAI (mean ± SD)‡			
Activity	15.3 ± 16.6	16.7 ± 14.2	0.670
Damage	1.9 ± 2.4	1.7 ± 2.4	0.718
Baseline PDAI banding, *Boulard 2016* (#, %)	--	--	0.227
None (0)	0 (0)	1 (1.2)	--
Moderate (1-15)	23 (62.2)	37 (45.1)	--
Significant (16-45)	6 (16.2)	24 (29.3)	--
Extensive (>45)	3 (8.1)	3 (3.7)	--
Baseline PDAI banding, *Shimizu 2014* (#, %)	--	--	0.805
Mild (0-8)	13 (35.1)	22 (26.8)	--
Moderate (9-24)	13 (35.1)	29 (35.4)	--
Severe (>24)	6 (16.2)	14 (17.1)	--
Baseline PDAI banding, *Hébert 2018* (#, %)	--	--	0.199
PDAI 0-15	23 (62.2)	38 (46.3)	--
PDAI 16+	9 (24.3)	27 (32.9)	--

Abbreviations: PDAI, Pemphigus Disease Area Index
*Steroid-sparing therapy consisted of mycophenolate, methotrexate, azathioprine, or dapsone
†Includes pemphigus erythematosus and paraneoplastic pemphigus
‡Due to missing data, SST n=32 and no SST n=65

significant. For survival-type endpoints, we estimated survival distributions using Kaplan-Meier's method, with comparisons between treatment groups utilizing the log-rank test.

RESULTS

Of 119 pemphigus patients included in this study, 37 received rituximab with SST, and 82 received rituximab without SST. SST consisted of mycophenolate, methotrexate, azathioprine, cyclosporine, dapsone, sulfasalazine, 6-thioguanine, or intravenous immunoglobulin. Mean age (53.3 ± 16.2 vs 52.1 ± 15.5, *P*=0.710) and sex distribution (62.2% vs 59.8% female, *P*=0.842) did not differ between the SST and no-SST groups (Table 1). Pemphigus vulgaris was the most common diagnosis in both groups (67.6% vs 76.8%, *P*=0.268; Table 1). Prior to rituximab therapy, patients who received SST had a longer duration of disease (6.31 ± 8.8 years vs 2.81 ± 4.5 years, *P*=0.006). The average PDAI activity score for patients with and without SST was 15.3 ± 16.6 and 16.7 ± 14.2 (*P*=0.670), respectively, with no difference in disease severity per published disease severity classification scores (Table 1).[7-9] There was no difference between prednisone dose at the time of rituximab treatment between patients on and off SST. Following rituximab therapy, there was no difference in time to remission (*P*=0.507; Figure 1A), time to prednisone dose of 10 mg or less (*P*=0.743; Figure 1B), time to cessation of prednisone therapy (*P*=0.289; Figure 1C), or time to relapse (*P*=0.430; Figure 1D). No significant difference was noted in the number of serious adverse events between groups.

doi:10.36849/JDD.7949e

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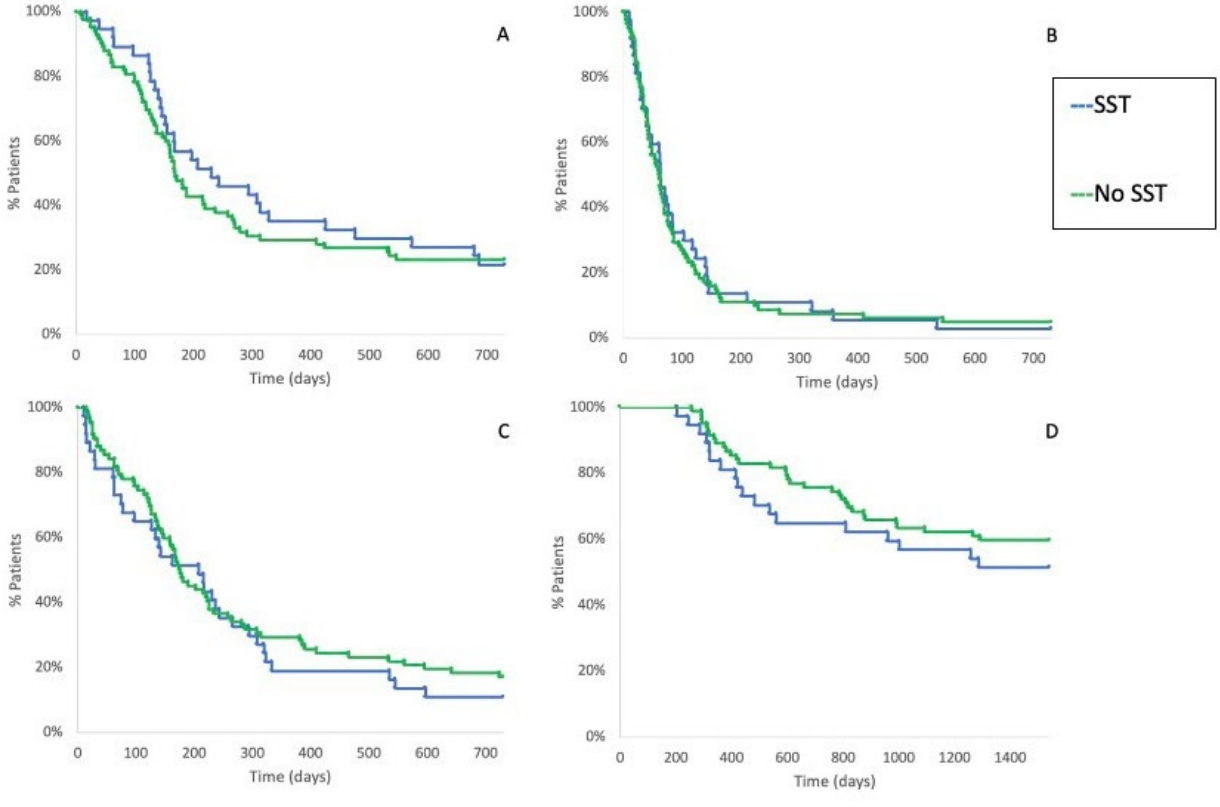
FIGURE 1. Kaplan-Meier regression curves from time of rituximab dosing demonstrate no statistical difference in (A). Time to remission (B). Time to prednisone dose ≤ to 10 mg (C). Time to cessation of prednisone therapy (D). Time to relapse.



CONCLUSION

Our results indicate that the use of SST with rituximab dosing did not improve clinical outcomes related to time to remission, reduction in prednisone dosing, or relapse. While the cohort on SST had a longer disease duration, it is not clear whether continuing SST with rituximab dosing confers any additional benefit. These data provide further evidence for not adding and/or discontinuing SST with rituximab therapy in most patients with pemphigus. Limitations include a high proportion of patients with moderate disease, a retrospective analysis, and a single academic center. Further clinical trials are needed to confirm the appropriate rituximab dosing schedule for induction of long-term remission.

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.2024.NVRN0324

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FEATURED CONTENT

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NEWS, VIEWS, & REVIEWS

Highlighting the Link Between Lichen Planus Pigmentosus and Frontal Fibrosing Alopecia

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BACKGROUND

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia, considered a variant of lichen planopilaris due to histological similarities.[1] Clinically, FFA causes gradual hair loss of the frontotemporal hairline and is commonly associated with loss of eyebrows and body hair. FFA may occur in conjunction with lichen planus pigmentosus (LPPigm), another lichenoid condition (Figure 1). LPPigm is a macular variant of lichen planus that presents as diffuse or reticulated grey to brown macules on sun-exposed areas and in flexures, eventually evolving into large hyperpigmented patches.[2] LPPigm mainly affects the face and neck but can sometimes progress to the trunk and upper limbs and may be associated with a burning sensation or itch.[3] There is limited data regarding the association between these two conditions, though various reports have documented a link.[4-8]

Figure 1. Typical clinical presentations of frontal fibrosing alopecia, with band-like recession of the frontotemporal hairline, and lichen planus pigmentosus, with hyperpigmented patches affecting the forehead **(A, B, C, D)**.

Epidemiology

Concomitant FFA and LPPigm most commonly affects dark skinned individuals, with one case series describing its occurrence in 5 women with skin phototypes II and III.[9] The first study associating both conditions evaluated 24 patients from South Africa, with 91% of patients identifying as African.[4] Subsequent reports similarly noted its association in dark skinned patients.[6,7,10] More recently, a multicenter retrospective descriptive analytical study involving 104 patients with combined FFA and LPPigm found that most affected patients had skin phototypes IV, V, and VI (74.1%).[5] Data regarding whether LPPigm precedes FFA is conflicting. In the patient cohorts evaluated by Dlova et al and Romiti et al, LPPigm preceded FFA in all patients, with an average lag time of 14 and 10 months respectively between each diagnosis.[4,7] These case series consisted of smaller cohorts, involving 24 and 16 patients respectively. The observed trend was less pronounced in the larger, multicenter study, with LPPigm preceding FFA in 56.8% of cases[5] and 51% of cases in another case series of 37 patients.[6] Though there is inconsistent evidence elucidating the temporal relationship between LPPigm and FFA, LPPigm appears to precede FFA in some patients, and is thus a proposed risk factor for FFA.[4] Most studies have reported a larger frequency of concomitant FFA and LPPigm in post-menopausal women,[5-7] which is consistent with the general FFA epidemiology.[5] In Dlova et al's study, most patients were premenopausal. Increased mechanical trauma associated with hair grooming styles is a potential explanation for the relatively early manifestation of FFA in African patients.[4]

Pathophysiology

A continual inflammatory response and breakdown of immune privilege of the epithelial hair follicle stem cells is pivotal in the pathogenesis of FFA. CD8+ T-lymphocytes and IFN-γ are key mediators of the associated inflammatory processes.[11,12] The pathogenesis of LPPigm remains unclear, though it is known that CD8+ T-lymphocytes and mediators such as interferon-gamma, tumor necrosis factor-alpha, interleukin 6, and lymphocyte function-associated antigen 1 play a role.[11,3] The clinical parallelism and progression between LPPigm and FFA, and their histological associations suggest that LPPigm and FFA represent distinct stages within the spectrum of the same underlying disease,[4] though more research is necessary to evaluate the association.

Treatment

FFA is a chronic condition, requiring long-term treatment, often with a combination of therapies. Commonly prescribed topical

medications include corticosteroids, minoxidil, and calcineurin inhibitors. Topical treatment involves the whole scalp due to possible follicular inflammation in the unaffected scalp.[13] Systemic treatments include 5-alpha reductase inhibitors, hydroxychloroquine, and retinoids. Table 1 highlights treatments supported by published data, though smaller studies have highlighted the utility of pioglitazone, methotrexate, naltrexone, and hair transplantation.[14] There are currently no approved or validated treatments due to a paucity of randomized trials. Topical treatments for LPPigm include high potency steroids, tacrolimus, and skin lightening creams. Systemic treatments include isotretinoin, tranexamic acid, and vitamin A. Laser treatments and chemical peels are another option, though expensive. Notable studies are highlighted in Table 2. A combination of topical and systemic treatments, robust sunscreen application, and trigger avoidance is likely to yield the best outcomes.[15] Treatment for both FFA and LPPigm centers around slowing or preventing progression, and there is a low threshold for starting systemic therapies for patients who prefer an aggressive approach.

Table 1. Efficacy of Treatment Approaches for Frontal Fibrosing Alopecia[14]

Treatment	Study Type	Patients (n)	Treatment Regimen	Duration	Response
Topical steroids	Retrospective cohort study[16]	48	Clobetasol propionate or betamethasone valerate 3 times per week, pimecrolimus 1% 3 times per week	20 months	Improvement 39.6%, stabilized 25%, no improvement 22.9%
Topical minoxidil	Retrospective cohort study[17]	2	Topical 2% minoxidil solution	Unspecified	No improvement
Intralesional Steroids	Retrospective cohort study[18]	130	Injections every 3 to 6 months, average of 8 injections per patient	Unspecified	Regrowth 34%, stabilized 49%, no improvement 5%, unavailable results 12%
Hydroxychloroquine	Retrospective cohort study[18]	54	Hydroxychloroquine 200-400 mg/day with nonspecific therapies	Unspecified	Regrowth 15%, stabilized 59%, no improvement 22%, unavailable results 4%
Finasteride	Retrospective cohort study[18]	102	Finasteride 2.5-5 mg/day	Unspecified	Regrowth 47%, stabilized 53%
Dutasteride	Retrospective cohort study[19]	13	Dutasteride 0.5 mg/day	12 months	Regrowth 15%, stabilized 46%, slow progression 38%; no recurrence in responders at 18 months
Systemic retinoids	Retrospective cohort study[20]	29	Isotretinoin 20 mg/day	12 to 16 months	Stabilized 79%

Table 2. Efficacy of Treatment Approaches for Lichen Planus Pigmentosus

Treatment	Study Type	Patients (n)	Treatment Regimen	Duration	Response
Tacrolimus ointment	Open label, non-randomized, prospective study[22]	13	Topical tacrolimus 0.03% twice daily	6 to 12 weeks	Cessation of disease progression and reduction of pigmentation in all patients
Tacrolimus ointment + dapsone	Retrospective cohort study[23]	5	Topical tacrolimus 0.1% ointment twice daily and oral dapsone 100mg/day	Unspecified	Partial improvement 50%, no improvement 15%, reduced pruritus 45%, lost to follow up 35%
Oral tranexamic acid	Prospective study[24]	20	Oral tranexamic acid 250 mg/day; sunscreen strongly encouraged	4 to 6 months	Moderate improvement 55.7% (26-50%), good improvement 21.8% (>50%), and mild improvement 6.2% (<25%) in intensity and progression of pigmentation; 11% without improvement
Isotretinoin	Open label, non-randomized, prospective study[25]	27	Oral isotretinoin 20 mg/day and sunscreen	6 months	1-3 courses (n=44): Good improvement 11.4%,
Vitamin A	Prospective pilot study[26]	140	Vitamin A 100,000 units/day daily	15 days, followed by a 15 day washout period; treatment course then repeated with variable frequency	4-6 courses (n=19): good to excellent improvement 31.6%,
Nd:YAG laser	Prospective pilot study[27]	9	1064 nm Q-switched Nd:YAG laser 6mm spot, fluence 3 J/cm^2 and 10-Hz frequency plus toning every 2 weeks	6 sessions	7-9 courses (n=15): good to excellent improvement 44.4%,
Nd:YAG laser	Open label, non-randomized prospective pilot study[27]	13	1064 nm Q-switched Nd:YAG laser 5 mm spot, fluence 3-4.6 J/cm^2 and 5-Hz frequency, with periodic fluence increase	Every 4 to 8 weeks, 5 to 6 sessions on average	10 or more courses (n=12): good to excellent improvement 75%,
Phenol peels	Retrospective cohort study[28]	17	Croton oil free phenol combination every 3 weeks	6 sessions	35.7% lost to follow-up

Clinical Considerations

FFA and LPPigm are difficult to treat and can be distressing for patients, especially when coexisting. The loss of follicular ostia in FFA is irreversible, and thus dermatologists need to diagnose and treat it early. Clinicians should be aware of the overlap between FFA and LPPigm and examine patients with LPPigm for FFA and vice versa, especially in patients with darker skin tones.[10] As LPPigm frequently precedes FFA, its presence may serve as an early indicator of FFA onset and should prompt further evaluation. When coupled with other severity indicators of FFA, such as facial papules and the loss of eyebrows and eyelashes, concurrent LPPigm can be regarded as an adverse prognostic factor.[5]

Disclosure

SAA's work is funded through independent fellowship grants from Lilly and Pfizer; CW's work is funded through an independent fellowship grant from Galderma.

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