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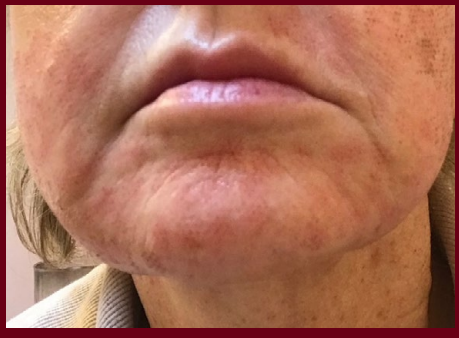

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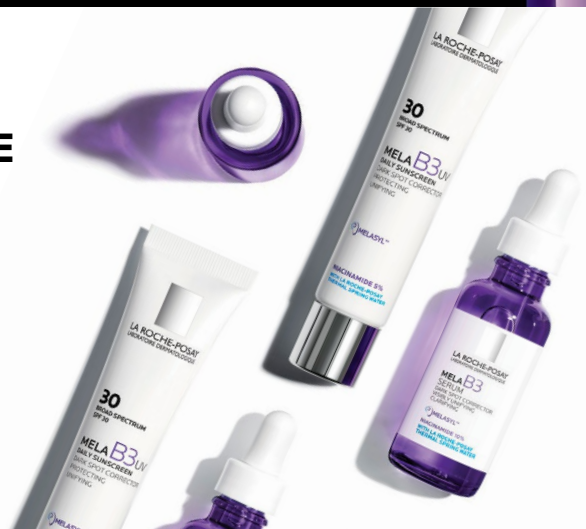

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy and Tolerability of Topical 0.1% Stabilized Bioactive Retinol for Photoaging: A Vehicle-Controlled Integrated Analysis

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ABSTRACT

Introduction: Chronic exposure to ultraviolet light photoages skin. Retinol, a precursor molecule to retinoic acid that causes less irritation, is available as a nonprescription, cosmetic retinoid and improves collagen production, skin elasticity, and signs of photoaging. Advances in formulation science have allowed the production of stabilized bioactive retinol formulations. This integrated analysis aims to build on previous studies and further examine the comprehensive efficacy and tolerability of topical 0.1% stabilized bioactive retinol.

Methods: This analysis included 6 vehicle-controlled studies of 0.1% stabilized bioactive retinol in women with mild-to-moderate signs of photodamage. Across all studies, the same dermatologist investigator assessed overall photodamage; wrinkles on the forehead, cheeks, and undereye area; crow's feet wrinkles and fine lines; lack of even skin tone; and brown spots at baseline and weeks 4, 8, and 12 on a numerical scale. Tolerability was also assessed.

Results: Participants (retinol, N=237; vehicle, N=234) had a mean (SD) age of 47.4 (6.6) years. Retinol induced greater improvements from baseline in all signs of photoaging vs vehicle as early as week 4 and through 12 weeks of application. Few participants experienced irritation; all events were mild to moderate and transient. The most common signs of irritation were erythema (n=2) and skin scaling/peeling (n=5).

Conclusions: This pooled analysis of 6 vehicle-controlled clinical studies provides new evidence for the efficacy of 0.1% stabilized bioactive retinol in improving signs of photoaging without causing major irritation. Topical 0.1% stabilized bioactive retinol was well tolerated with only a few reported cases of skin irritation.

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INTRODUCTION

Chronic exposure to ultraviolet light compromises the structural integrity of the skin and results in premature signs of aging, including facial fine lines and wrinkles, lack of even skin tone, brown spots, and overall photodamage. Collectively, these changes are referred to as photoaging.[1,2]

Cosmetic and prescription retinoids are used to improve the visible signs of a variety of dermatoses, including photoaging.[3,4] Retinoic acid is the most active form of vitamin A within the cell, and after binding to nuclear receptors, retinoic acid directly or indirectly induces the expression of genes involved in cellular proliferation and differentiation.[4-6] Retinoids are widely used to improve the signs of photoaging, and their benefits have been confirmed in numerous well-designed studies.[7-10] Unfortunately, prescription retinoids, such as retinoic acid, can lead to skin irritation (including erythema, burning, and scaling), referred to as retinoid dermatitis,[11] and they are less accessible than nonprescription, cosmetic retinoids.

Precursors to retinoic acid produce less skin irritation than retinoic acid because they are converted into retinoic acid by

rate-limiting enzymatic steps, limiting the amount of retinoic acid acting on the skin at any given time.[12] Retinol, a precursor molecule to retinoic acid, is available as a cosmetic retinoid and is metabolized within the skin into retinoic acid when applied topically.[13] Cosmetic retinoids, including retinol, have emerged as a solution for photoaging due to their improved tolerability and increased accessibility compared with prescription retinoids. Despite their benefits, some cosmetic retinoids have been associated with issues of low skin penetration.[14] Furthermore, retinoids are sensitive to light and oxidation and require proper packaging to prevent degradation.[1,13] To overcome these challenges, retinol must be uniquely formulated in a stabilizing vehicle to maximize the product's clinical effect while balancing the potential for irritation.

Advances in formulation science have allowed the production of uniquely stabilized and bioactive retinol formulations.[15] The bioactivity of retinol can be measured through cellular retinoic acid binding protein (CRABP-II) expression. CRABP-II is a highly sensitive marker for retinoid bioactivity; thus, CRABP-II gene expression correlates with retinol potency.[16] In an ex vivo study of human skin explants, 0.1% stabilized retinol induced CRABP-II and heparin-binding epidermal growth factor (HBEGF) expression and caused epidermal thickening. Participants who applied stabilized 0.1% retinol showed improved appearance of fine lines and skin tone evenness.[17] While the bioactivity of topically applied stabilized retinol has been demonstrated, the clinical efficacy of retinol is not yet widely appreciated among the dermatological community.

The efficacy and tolerability of 0.1% stabilized bioactive retinol have been shown in 2 double-blind trials.[7,18] In an 8-week, double-blind, split-face, vehicle-controlled study of 64 women aged 40–65 years with moderate photodamage, the use of 0.1% stabilized bioactive retinol significantly improved signs of photoaging vs vehicle.[18] In a double-blind, full-face, vehicle-controlled study of 67 women, the use of 0.1% stabilized bioactive retinol on photodamaged skin showed persistent statistically significant improvement in signs of aging vs vehicle over a 1-year study period.[7] To build on these previously published results and add to the body of literature for retinol, this integrated analysis examined the comprehensive efficacy and tolerability of 0.1% stabilized bioactive retinol in 6 vehicle-controlled clinical studies that used similar assessment scales graded by a single dermatologist investigator.

MATERIALS AND METHODS

Study Design

This integrated analysis combined results from 6 vehicle-controlled clinical studies (studies A–F) of 0.1% stabilized bioactive retinol vs vehicle that were conducted by a single dermatologist investigator (Table 1); studies B and F were previously published.[7,18] Studies A through E were split-face designs, with participants applying either retinol or vehicle to one half of their face (serving as their controls). In study F, participants were randomized to apply either retinol or vehicle to their entire face. All studies were at least 12 weeks in duration, except for study B, which was 8 weeks. Products were applied either once (studies B, C, E, and F) or twice daily (studies A and D).

Participants

Participants were healthy women aged 30 years and older with clinician-rated mild-to-moderate signs of photodamage (defined specifically as presence of wrinkles on forehead, crow's feet, upper lip, and nasolabial fold for study A; a score of 4–8 on a 0–9 scale for overall photodamage, crow's feet and upper cheek area wrinkles, and pigmentation for study B; signs of photodamage for studies C and D; and a score of 4–8 for overall photodamage,

TABLE 1.

Retinol Study Design and Participants

Study	Sample Size[a]	Age Range, Years	Fitzpatrick Skin Type	Design	Application Frequency	Duration	Study Visits (Weeks)
A	Retinol, n = 49 Vehicle, n = 49	≥ 40	NR	Split face	Twice daily	12 weeks	2, 4, 8, 12
B	Retinol, n = 28 Vehicle, n = 26	40–65	I–III	Split face	Once daily	8 weeks	4, 8
C	Retinol, n = 42 Vehicle, n = 42	35–60	NR	Split face	Once daily	12 weeks	Immediate,[b] 2, 4, 8, 10, 12
D	Retinol, n = 42 Vehicle, n = 42	30–55	NR	Split face	Twice daily	12 weeks	4, 8, 12
E	Retinol, n = 40 Vehicle, n = 40	35–59	I–III	Split face	Once daily	12 weeks	2, 4, 12
F	Retinol, n = 32 Vehicle, n = 32	40–55	I–III	Full face	Once daily	12 weeks	4, 8, 12[c]

NR, not reported.
[a]Includes participants with data at baseline and after the 8-week or 12-week study period.
[b]5–10 minutes after the first application.
[c]Study F was 52 weeks in duration, but only the first 12 weeks were included in this analysis.

4–6 for crow's feet and undereye wrinkles, and 3–5 for mottled pigmentation for studies E [using a 1–9 scale] and F [using a 0–9 scale]). Participants were excluded if they were pregnant or breastfeeding. Participants were asked to discontinue the use of all antiaging products 1 month before the baseline visit, wash their face with their current facial cleanser, and avoid prolonged exposure to the sun for the length of the study period.

Assessments

Efficacy Assessments

Signs of photodamage were assessed by the dermatologist investigator and the participant at various timepoints across the studies. This analysis included investigator assessments only, and data were analyzed at weeks 4, 8, and 12. Photodamage assessments included overall photodamage; wrinkles on the forehead, cheek, and undereye; crow's feet wrinkles and fine lines; lack of even skin tone; and brown spots. All efficacy assessments were scored using a 0–9 scale, except in study E, which utilized a 1–9 scale; this slight difference in scale was not expected to meaningfully impact mean treatment differences or population standard deviations.

Tolerability Assessments

Tolerability assessments were performed at baseline and weeks 4, 8, and 12 in all 12-week studies and at weeks 4 and 8 in study B. At each assessment, the dermatologist investigator rated participants' skin for erythema, scaling/peeling, and edema using Likert-type scales. Two studies utilized a 0–3 scale (mild = 1, moderate = 2, and severe = 3), and 4 studies used a 0–9 scale (mild = 1–3, moderate = 4–6, and severe = 7–9).

Statistical Analysis

Efficacy results are presented as mean change from baseline and as the overall effect of retinol vs vehicle. For between-treatment efficacy assessments, by-study estimated treatment differences and SE were calculated consistently with the original individual study analyses. Specifically, estimates corresponding to Student's t-tests were used for all studies, except for study A, which used estimates corresponding to a paired t-test. Within-treatment efficacy assessments were based on mean and SE for change from baseline for each study. Meta-analyses for between treatment and within-treatment assessments used fixed-effects meta-analysis methodology and were based on the weighted means of the within-study differences. Tolerability results were summarized as the frequency of participants who experienced signs of irritation (erythema, scaling/peeling, and edema) at 4, 8, and 12 weeks.

RESULTS

Participants

Among 352 participants (including the total number of participants who applied retinol [N = 237] or vehicle [N = 234] in either a split-face or entire-face study design), baseline age, skin type, and signs of photoaging were balanced between retinol and vehicle (Table 2). The mean (SD) and median (range) age of participants were 47.4 (6.6) years and 47.0 (30–72) years, respectively. Among participants for whom skin type was recorded (n = 142), most (n = 115) had Fitzpatrick skin type III. Mean baseline scores for signs of skin aging reflected mild-to-moderate photodamage.

Efficacy Assessments

Retinol resulted in greater decreases from baseline in overall photodamage compared with vehicle at weeks 4, 8, and 12 (Figure 1A). The effect of retinol (reported as the difference between the mean change from baseline [95% CI] for retinol and vehicle) for overall photodamage at week 12 was –0.88 (–0.98, –0.79; Figure 2A).

Similarly, retinol resulted in greater decreases from baseline in wrinkles on the forehead, cheek, and undereye and crow's feet wrinkles and fine lines compared with vehicle at weeks 4, 8, and 12 (Figure 1B–F). At week 12, the effect of retinol was –0.41 (–0.48, –0.33) for forehead wrinkles, –0.68 (–0.77, –0.59) for cheek wrinkles, –0.40 (–0.48, –0.32) for undereye wrinkles, –0.36 (–0.44, –0.27) for crow's feet wrinkles, and –0.90 (–1.00, –0.81) for crow's feet fine lines (Figure 2B–F).

TABLE 2.

Baseline Demographics and Clinical Characteristics[a]

Characteristic	Retinol	Vehicle
Age, years, median (range)	n = 209 48.0 (33–72)	n = 208 47.0 (30–72)
Fitzpatrick skin type, n (%)[b]		
I	2 (< 1.0)	2 (< 1.0)
II	11 (4.6)	12 (5.1)
III	61 (25.7)	59 (25.2)
Baseline signs of skin aging, mean (SD)		
Overall photodamage	n = 160 5.0 (0.7)	n = 159 5.0 (0.7)
Forehead wrinkles	n = 236 4.3 (1.0)	n = 233 4.4 (1.0)
Cheek wrinkles	n = 155 3.9 (1.0)	n = 153 4.0 (1.1)
Undereye wrinkles	n = 237 4.5 (0.9)	n = 234 4.4 (0.9)
Crow's feet wrinkles	n = 236 3.8 (1.3)	n = 233 3.8 (1.3)
Crow's feet fine lines	n = 236 3.8 (0.6)	n = 233 3.8 (0.6)
Lack of even skin tone	n = 208 4.3 (0.8)	n = 207 4.3 (0.7)
Brown spots	n = 236 2.9 (1.6)	n = 233 2.9 (1.6)

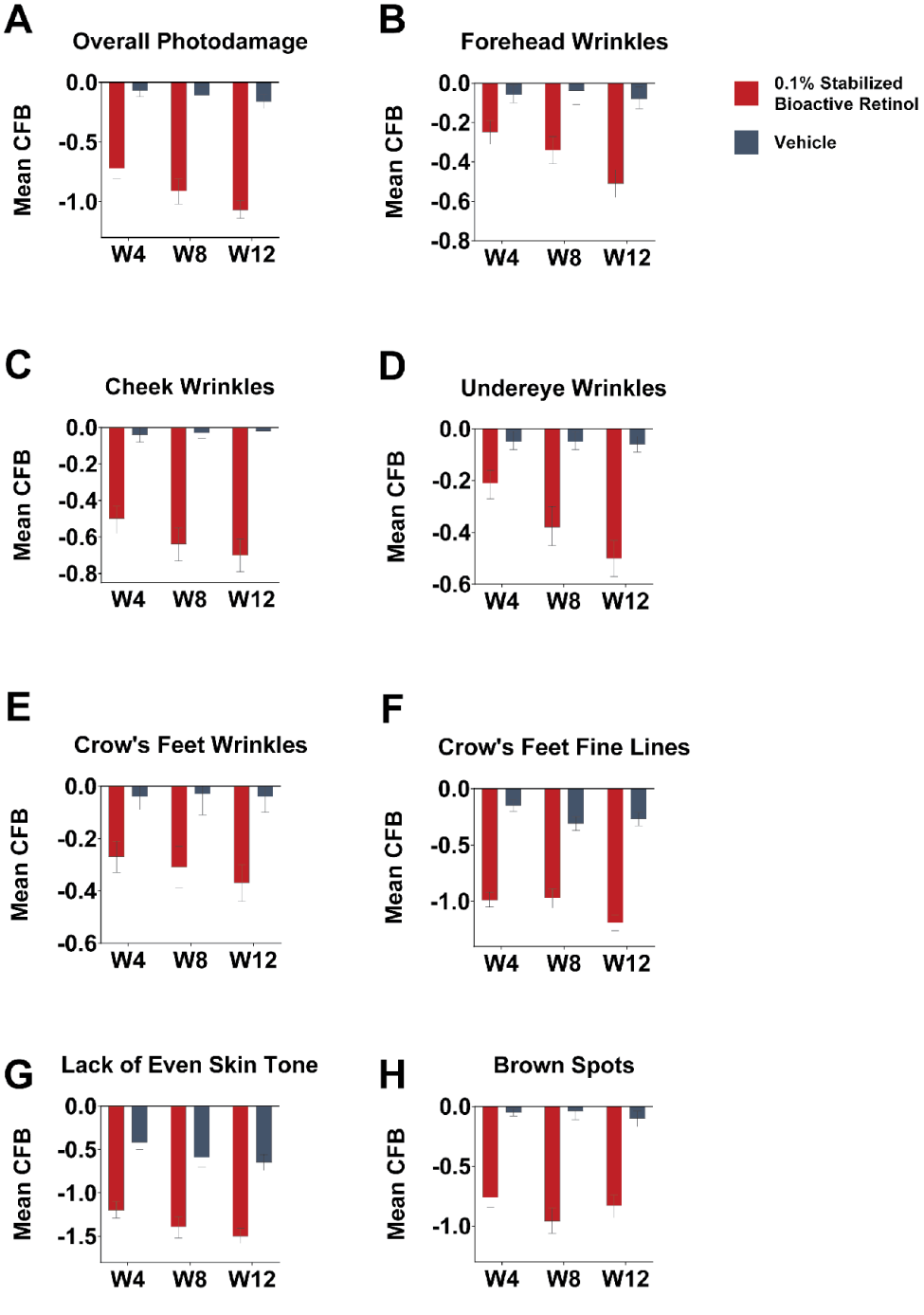
[a]Due to the split-face design of some of the included studies, participants may have used vehicle, retinol, or both. [b]Fitzpatrick skin type information was not reported for studies A, C, and D.

Retinol also resulted in greater decreases from baseline in uneven skin tone and brown spots compared with vehicle at weeks 4, 8, and 12 (Figure 1G and 1H). The effects of retinol for uneven skin tone and brown spots at week 12 were –0.83 (–0.95, –0.71) and –0.74 (–0.85, –0.63), respectively (Figure 2G and 2H).

Tolerability Assessments

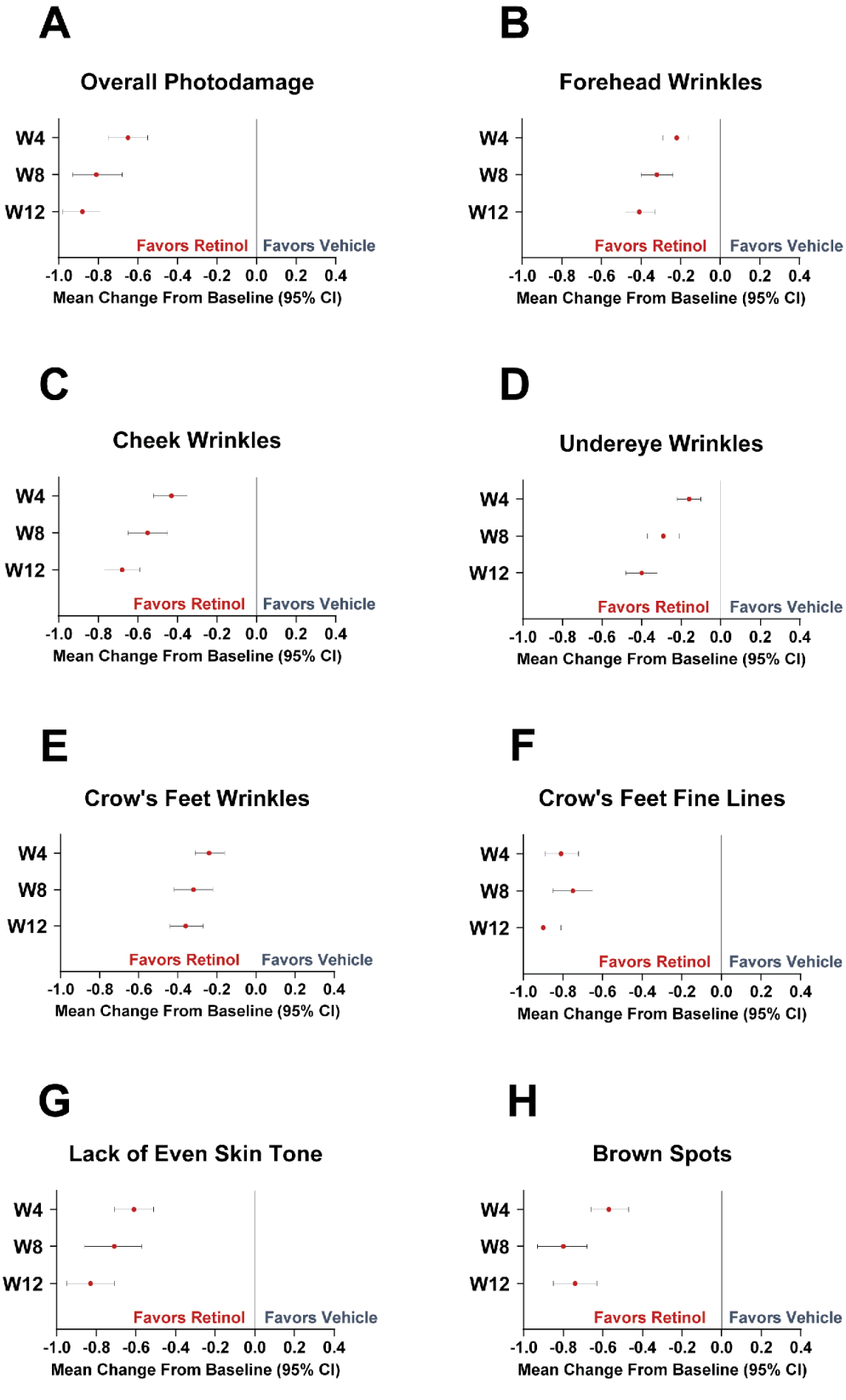
At week 4, 1 participant experienced moderate erythema with retinol, and 1 participant experienced mild erythema with vehicle; both cases resolved by week 8. Scaling/peeling was reported for 3 participants with retinol (2 mild, 1 moderate) and 2 participants with vehicle (both mild) at week 4; all cases resolved by week 8. Edema was not reported for any participants during the study period. Retinol and its vehicle were well tolerated up to 12 weeks, with no severe signs of irritation (Table 3).

FIGURE 1. Mean change from baseline over time for retinol vs vehicle in signs of photodamage. Error bars represent 95% CI.



CFB, change from baseline; W, week.

FIGURE 2. Effect of retinol vs vehicle over time for signs of photodamage.



W, week.

TABLE 3.

Tolerability of Retinol vs Vehicle Over Time

Tolerability Endpoints	Baseline		Week 4		Week 8		Week 12	
	Retinol	Vehicle	Retinol	Vehicle	Retinol	Vehicle	Retinol	Vehicle
Erythema, n (%)								
None	187 (100)	187 (100)	151 (99.3)	149 (99.3)	112 (100)	110 (100)	155 (100)	155 (100)
Mild	0	0	0	1 (< 1.0)	0	0	0	0
Moderate	0	0	1 (< 1.0)	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Scaling/Peeling, n (%)								
None	187 (100)	184 (100)	149 (98.0)	148 (98.7)	112 (100)	110 (100)	155 (100)	155 (100)
Mild	0	0	2 (1.3)	2 (1.3)	0	0	0	0
Moderate	0	0	1 (< 1.0)	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Edema, n (%)								
None	187 (100)	184 (100)	152 (100)	150 (100)	112 (100)	110 (100)	155 (100)	155 (100)
Mild	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0

Tolerability data from all 6 studies. Two studies used a 0–3 scale (mild = 1, moderate = 2, and severe = 3), and 4 studies used a 0–9 scale (mild = 1–3, moderate = 4–6, and severe = 7–9).

DISCUSSION

Retinoic acid is commonly prescribed by dermatologists to improve the clinical signs of photoaging; however, its significant potential for irritation and prescription-only status limit the number and type of individuals for whom it is a viable treatment option.[13,14] Retinol is a bioactive precursor of retinoic acid that is available without a prescription and, when uniquely formulated to be stabilized and bioactive, can improve the signs of photoaging with less skin irritation. The efficacy of 0.1% stabilized bioactive retinol was previously demonstrated in an 8-week, double-blind, split-face, vehicle-controlled study of 64 women (study B) and in a 52-week, full-face, vehicle-controlled study of 67 women (study F).[7,18] However, these published data on the efficacy and tolerability of retinol were limited to relatively small populations. Therefore, in this integrated analysis, which stands as one of the largest, vehicle-controlled analyses of retinol to date, we examined the efficacy and tolerability of topical 0.1% stabilized bioactive retinol in a larger pooled population of participants.

We integrated data from 6 randomized, vehicle-controlled trials of more than 350 participants conducted by a single dermatologist investigator with similar methods. The results confirm previous findings[7,18] and further demonstrate the efficacy and tolerability of topical 0.1% stabilized bioactive retinol in those with mild-to-moderate photodamage. In this analysis, improvements from baseline in overall photodamage, wrinkles, lack of even skin tone, and brown spots were observed with 0.1% stabilized bioactive retinol compared with vehicle as early as week 4 and through all evaluated timepoints (week 8 or 12). Similar and low (≤ 2%) incidence of erythema, scaling/peeling, and edema were observed for both retinol and vehicle, and investigator-reported signs of irritation were transient (reported at week 4 but resolved by week 8) with none being severe.

Limitations of this analysis should be acknowledged. The study assessed outcomes in a homogenous study population, which included only women aged ≥ 30 years with Fitzpatrick skin types I–III as those participants are most likely to exhibit fine lines and wrinkles at this age range.[19] While an inherent limitation of using pooled analyses is the risk of bias from 1 or more studies based on differing methodologies,[20] the studies used in this analysis were selected because of the similarities in study design (inclusion of vehicle control and the same concentration of stabilized retinol) and assessments (evaluations performed by a single dermatologist investigator across all 6 studies and use of similar grading scales). The difference in the numerical scale between study E (1–9) and the other studies (0–9) was not expected to have a meaningful effect on treatment differences.

CONCLUSION

At the time of this publication, our analysis represents one of the largest datasets demonstrating the clinical benefit and tolerability of retinol. This pooled analysis of 6 vehicle-controlled clinical studies provides new evidence on the efficacy of once- or twice-daily application of topical 0.1% stabilized bioactive retinol in improving signs of photoaging without causing major irritation. Improvements in photoaging were observed

as early as 4 weeks and were maintained through 12 weeks. Additionally, only a few participants using topical 0.1% stabilized bioactive retinol experienced irritation, with the most common events being erythema and skin scaling/peeling. These pooled results demonstrate that a well-formulated topical retinol at a strength of 0.1% can be an effective cosmeceutical solution for individuals seeking to improve signs of photoaging.

DISCLOSURES

Patricia Farris serves as a consultant/advisory board member for AlumierMD, Cerave, Fig.1 Skincare, Kenvue, La Roche Posay, Love My Delta, Nutraceutical Wellness, Pierre Fabre, Skinceuticals, U.SK Under Skin, Vichy. She is cofounder and stockholder of RegimenMD. Diane Berson is a consultant and/or serves on advisory boards for Allergan, Almirall, Cassiopea, Crown, Kenvue, L'Oréal, La Roche-Posay, Ortho Derm, Regimen Pro, Revance, TopMD, and Sente. Neal Bhatia is an advisor, consultant, investigator, and/or speaker for AbbVie, Almirall, Arcutis, Advanced Derm Solutions, Amytrx, Beiersdorf, Biofrontera, BMS, BI, Cara Therapeutics, Castle, Dermavant, Ferndale, Foamix, Galderma, Incyte, ISDIN, J&J, La Roche Posay, LEO, Lilly, Mindera, Novartis, Ortho, Pfizer, Procter & Gamble, Regeneron, Sanofi, Skinfix, Soligenix, SunPharma, Verrica Pharmaceuticals, and Zerigo Health. David Goldberg has participated in the Merz speakers' bureau and has been awarded research grants by Allergan, Galderma, and Merz. He has served on advisory boards for Kenvue. Edward Lain is an advisor, speaker, and/or consultant for AbbVie, Alchemee, Almirall, DermaVant, Eli Lilly, EPI Health, Galderma, Incyte, Kenvue, L'Oréal, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB. Kavita Mariwalla is a consultant for Kenvue and L'Oréal brands; has served as a principal investigator for AbbVie and Merz; and has received honoraria from AbbVie, Galderma, Merz, and Unilever. Joshua Zeichner is an advisor, consultant, and/or speaker for AbbVie, Allergan, Arcutis, Dermavant, Galderma, Incyte, Kenvue, L'Oréal, Ortho Dermatologics, Pfizer, Procter and Gamble, Regeneron, RoC Skincare, Sun Pharma, UCB, and Unilever. Dara Miller, Tony McGuire, and Menas Kizoulis are employees of Kenvue and may own stock or stock options.

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ORIGINAL ARTICLE

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Treatments for Moderate-to-Severe Acne Vulgaris: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background: Multiple treatment options exist for the management of moderate-to-severe acne. However, the comparative effectiveness (efficacy/safety) of moderate-to-severe acne treatments has not been systematically examined.

Methods: A systematic literature review (SLR) was conducted to identify randomized controlled trials of ≥4 weeks of treatment (topical, oral, physical, or combinations) for moderate-to-severe facial acne in patients aged ≥9 years. Efficacy outcomes included: percentage of patients achieving ≥2-grade reduction from baseline and "clear" or "almost clear" for global severity score (treatment success); absolute change in inflammatory (ILs reduction); and noninflammatory lesion counts (NILs reduction). A random-effects network meta-analysis (NMA) was conducted for the efficacy outcomes. Treatments were ranked with posterior rank plots and surface under cumulative ranking values.

Results: Eighty-five studies were included in the SLR/NMA. Topical triple-agent fixed-dose combination (FDC) gel (clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%) and combinations of double-agent fixed-dose topical treatments with oral antibiotics (TOA3) consistently ranked in the top 3 treatments. Topical triple-agent FDC gel was numerically superior to TOA3 for treatment success (log-odds ratios: 1.84 [95% credible interval (CrI) 1.36 to 2.29]) and 1.69 (95% CrI: 1.01 to 2.32) vs placebo/vehicle). TOA3 was numerically superior to topical triple-agent FDC gel for reduction of ILs (mean difference: -8.21 [-10.33 to -6.13]) and -10.40 [-13.44 to -7.14] vs placebo/vehicle) and NILs (mean difference: -13.41 [-16.69 to -10.32] and -17.74 [-22.56 to -12.85] vs placebo/vehicle).

Conclusions: Based on this SLR/NMA, topical triple-agent FDC gel was the most efficacious and safe treatment for moderate-to-severe acne.

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INTRODUCTION

Acne vulgaris (acne) is an inflammatory cutaneous disorder of the pilosebaceous unit of the skin that leads to the development of whiteheads, blackheads, papules, pustules, nodules, and cystic lesions.[1] It is the most commonly diagnosed skin condition in the United States (US), predominantly among adolescents and young adults in their twenties.[1,2] The estimated prevalence in the US is 30.2 per 1,000 people, with more than 8 million cases.[3] Annual direct medical costs of acne in the US in 2013 were $846 million and the opportunity costs were $398 million.[4]

Guidelines from the US, Canada, and Europe recommend topical combination treatments, with consideration of oral drugs, as the first-line approach in moderate-to-severe acne.[5-8] Topical benzoyl peroxide (BPO), topical retinoids, topical antibiotics, and systemic drugs are all effective, but there is a lack of clarity about the most efficacious acne treatment.[9] Four systematic literature reviews (SLRs) and network meta-analyses (NMAs) have examined the relative efficacy of the numerous acne treatments.[8,10-12] Two were specific to patients with mild-to-moderate acne,[10,11] and the other 2 included patients with any severity of acne.[8,12] No SLR/NMA has specifically addressed

patients with moderate-to-severe acne, despite this subgroup bearing a greater disease and economic burden.[8,13] The purpose of this SLR/NMA was to evaluate the relative efficacy of available treatments for moderate-to-severe acne.

MATERIALS AND METHODS

Search Strategy

We searched the following literature databases (Figure 1): Ovid (MEDLINE), Ovid (EMBASE), Cochrane Central, PubMed, the National Health Service Economic Evaluation Database (NHSEED), and the Pediatric Economic Database Evaluation (PEDE). We searched the following health technology assessment databases: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Medicines Consortium (SMC), and the International Network of Agencies for Health Technology Assessment (INAHTA). We also searched trial registries (clinicaltrials.gov and EU Clinical Trials Register) and conference abstracts (American Academy of Dermatology [AAD], International Society of Dermatology [ISD], International Society for Pharmacoeconomics and Outcomes Research [ISPOR], and Northern Light Life Sciences). All searches spanned from inception until February 2023. We also screened citations in previously published SLRs and NMAs and cross-verified using Retraction Watch Database Version 1.0.6.0 for studies retracted due to compromised methodology.[14] The MeSH and EMTREE terms used for conducting the search, along with the search strategy, are provided in Appendix S1. (All appendices are available at: https://jddonline.com/wp-content/uploads/2024/03/M8148_Supplementary-data_JDD.pdf.)

Study Selection

Population

The SLR/NMA included studies based on a quantitative and qualitative approach to lesion counts and global assessment of acne severity. The US Food and Drug Administration (FDA) guidance[15] recommends using diagnostic scales for new drug approvals that encompass numbers and types of acne lesions as well as disease severity, such as Investigator's Global Assessment (IGA) and equivalent scales like Evaluator's Global Severity Scale (EGSS) and Investigator's Static Global Assessment (ISGA).[16] As the first scale, (IGA) was described by the FDA in 2005[17]; studies published prior to 2005 did not use these scales and hence were excluded. We included studies with male and female patients aged ≥9 years, diagnosed with moderate-to-severe facial acne (IGA/EGSS/ISGA: 3 [moderate] or 4 [severe]) at baseline. We excluded treatments with only a single randomized, controlled trial (RCT) because drug development for acne typically uses at least 2 RCTs.[18] The SLR/NMA included RCTs (phase 2, phase 3, parallel, or cross-over) and pooled studies (if the primary publication was not available). We included English-language RCTs with ≥50 patients in each arm, to minimize small sample bias and uncertainty in estimates.[8] The full inclusion/exclusion criteria are provided in the Appendix S2.

Treatments

We considered the following treatments based on AAD guidelines[19]:

- Monotherapy:
  - Topical (BPO, antibiotic, or retinoid)
  - Oral (antibiotic, retinoid, spironolactone, or contraceptive)
- Combination treatment:
  - Topical combinations
  - Topical triple-agent fixed-dose combination (FDC) gel
  - Topical double-agent FDCs
  - Pharmacologic + physical treatment
  - Topical + oral treatment
  - Other combinations
- Physical treatment:
  - Chemical peels
  - Comedone extraction
  - Photothermal therapy
  - Photochemical therapy
  - Photothermal + photochemical therapy
  - Photodynamic therapy
  - Photopneumatic therapy
  - Radiofrequency therapy
- Other treatments
  - Combined oral contraceptives
  - Metformin[20]

Outcomes

As per regulatory guidance,[15,16] efficacy outcomes were based on both quantitative and qualitative evaluation of acne. Hence, we included 3 outcomes: percentage of patients who achieved ≥2-grade reduction from baseline and "clear" or "almost clear" in IGA/EGSS/ISGA ("treatment success"); absolute change from baseline in inflammatory lesion counts ("ILs reduction"); and absolute change from baseline in noninflammatory lesion counts ("NILs reduction").

Citation Screening Process

We double-screened publications against eligibility criteria at 2 stages: title/abstract screening and full-text screening. A senior author resolved any disagreements. We used EndNote 20 (Clarivate, London, UK) to manage citations from search results, DistillerSR (DistillerSR Inc, Ottawa ON) for removing duplicates and screening citations, and MS-Excel (Microsoft Corporation, Redwood WA) for data extraction.

Data Extraction

We structured the data extraction form based on the format and guidelines used in Cochrane treatment reviews.[21-23] We extracted intention-to-treat data, or completer data only if intention-to-

treat data were not available. We extracted data based on study characteristics, outcomes, adverse events, tolerability, and acceptability.

Base-Case Model

We conducted feasibility assessments for each outcome (Appendix S3).[24-26] Under the assumption that treatments within a group exhibit equivalent efficacy, we considered 2 models: one with random study effects and fixed class effects (RSFC), and another with fixed study effects and fixed class effects (FSFC). Treatment duration was considered as a covariate in this analysis, and the Deviance Information Criterion (DIC) and posterior residual deviance were used to identify the best-fitted model.[27] We ranked treatments with posterior rank plots and surface under cumulative ranking (SUCRA) values. We presented relative treatment effects in pairwise analyses as a log-odds ratio with a 95% credible interval (95% CrI) for binary outcomes and mean difference (95% CrI) for continuous outcomes (Appendix S4).

Inconsistency

We compared a base-case model that assumed consistency and a global inconsistency model that assumed unrelated mean effects (UME)[28] (Appendix S5). This comprehensive approach allowed us to identify data points that might drive inconsistencies.[28]

Bias Adjustment Model

We used bias adjustment models to account for bias in each domain of the Cochrane Risk of Bias Tool (V2.0).[29] We down-weighted studies with high or unclear risk of bias to mitigate the impact on overall results (Appendix S6 and S7).

Threshold Analysis

We conducted study-level threshold analysis[30] as an alternative to the GRADE system to assess the influence of the study biases and sampling variation on the NMA results. The analysis addressed the question, "To what extent would the evidence need to be altered for the recommendation to change?" (Appendix S8). Threshold analysis determines the amount of evidence necessary to change the confidence in the efficacy estimate, accounting for biases and sampling variation. This analysis also provides insights into the robustness, stability, and reliability of efficacy estimates when facing data changes that could impact threshold values.

Protocol

We registered the study protocol in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration id CRD42023430668). This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[31] and its extensions for reporting SLRs (PRISMA-S)[32] and NMAs (PRISMA-NMA).[33]

RESULTS

We screened 3417 records, assessed 1022 reports, and included 104 publications in the SLR. The reasons for exclusion are shown in Figure 1. We also identified 333 reports from other methods and included 2 non-duplicate publications from these methods in the SLR. From these publications, 85 RCTs met the inclusion criteria for the NMA.

Feasibility Assessment

The NMA included RCTs that used IGA/ISGA/EGSS scales, based on the assumption that the efficacy measured using these scales would be similar (refer to Appendix S9 and S10 for a list of included/excluded trials). Random-effects meta-analysis confirmed there was no statistically significant variability for treatment success across IGA/EGSS/ISGA scales (Appendix S3), justifying this approach. There was no statistically significant difference in effect sizes between vehicle and placebo groups, supporting the use of a single placebo/vehicle group in the NMA.

We observed significant differences in the baseline characteristics, especially in terms of gender and the percentage of patients with moderate severity. These variations were apparent both among different studies (Appendix S11) and within and between the treatment groups (Appendix S12). The mean age was approximately 20 years in most studies (Appendix S13) and exhibited minimal variation across studies.

We conducted a rapid review and meta-regression to find potential effect modifiers. A rapid review found conflicting evidence regarding the potential effects of age and sex as modifiers (Appendix S14). Body mass index, severity of disease, and family history were identified as potential treatment effect modifiers (Appendix S15). Meta-regression revealed statistically significant effects (*P* value $P<0.05$) of acne severity and duration of treatment for all 3 outcomes.

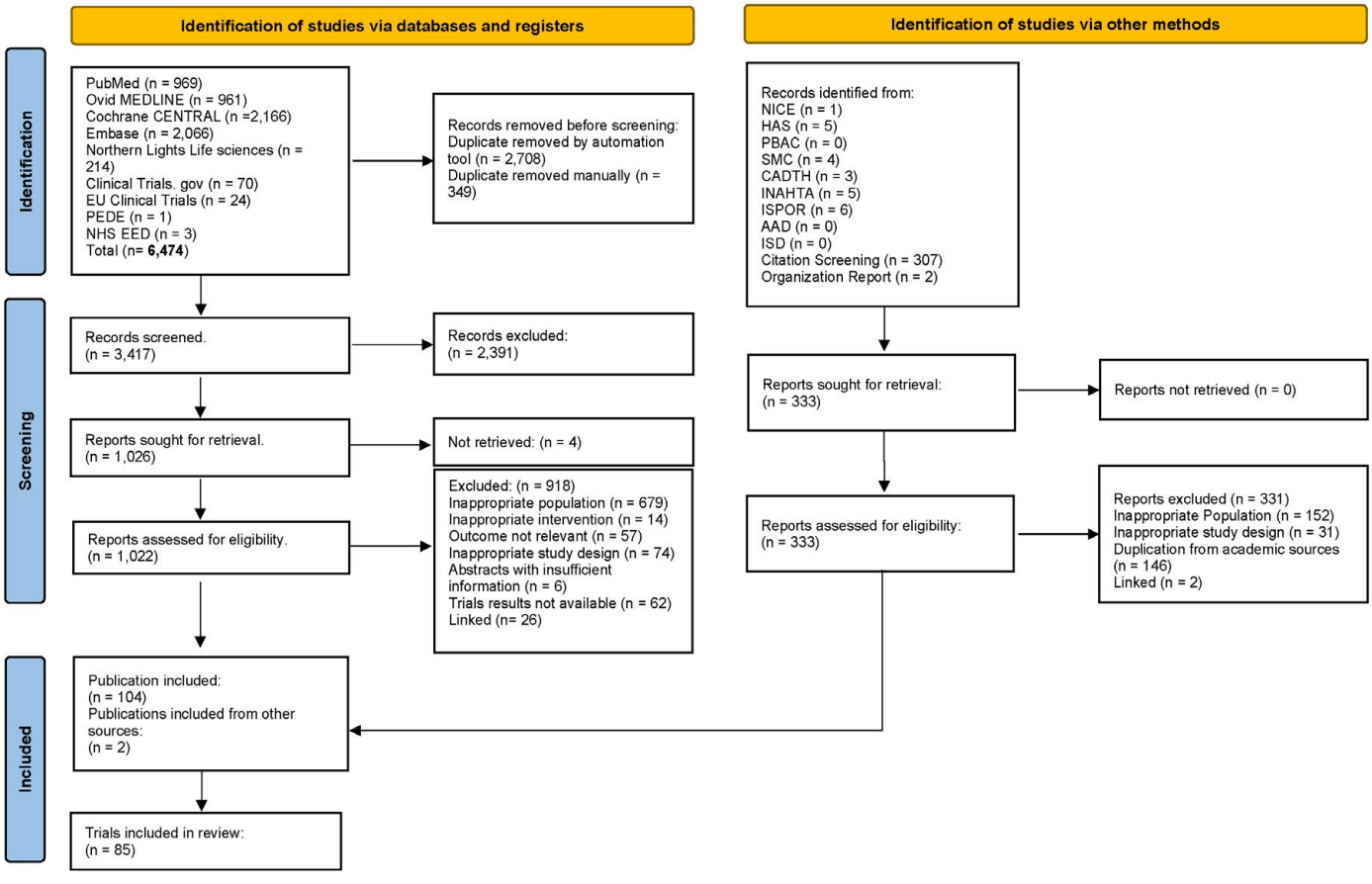
Model Fit

We chose the RSFC for each outcome based on the adequate fit of the posterior residual deviance and DIC (Appendix S16).

Treatment Success

Across 48 RCTs reporting treatment success (Appendix S17), 46 were multicenter studies and 28 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2A) and the number of patients ranged from 108 to 2,813 per study. Treatment characteristics and treatment success for included RCTs are listed in Appendix S17. The top 3 treatments for treatment success were: (1) topical triple-agent FDC gel (clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%[34]); (2) combinations of double-agent FDC topical treatments with oral antibiotic (TOA3); and (3) topical retinoid/BPO FDC (TFDCRB2). For these 3 treatments, log-odds ratios (95% CrI) compared with vehicle/placebo were 1.84 (1.36–2.29), 1.69 (1.01–2.32), and 1.36

FIGURE 1. Study selection process (PRISMA flowchart).



AAD, American Academy of Dermatology; CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; INAHTA, International Network of Agencies for Health Technology Assessment; ISD, International Society of Dermatology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NHS EED, National Health Services Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PEDE, Pediatric Economic Database Evaluation; SMC, Scottish Medicines Consortium.

(1.12–1.58), respectively (Figure 3A). Posterior ranks (95% CrI) were 1.49 (1–3), 2.28 (1–6), and 3.82 (2–6), respectively (Figure 4A) (Appendix S18). SUCRA probabilities were 96%, 88%, and 74%, respectively (Figure 5A).

Inflammatory Lesions Reduction

Across 50 RCTs reporting ILs reduction (Appendix S17), 47 were multicenter studies and 27 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2B), and the number of patients ranged from 107 to 2,813 per study. The top 3 treatments for ILs reduction were: (1) TOA3; (2) topical triple-agent FDC gel; and (3) topical antibiotic/BPO FDC (TFDCAB2). For these 3 treatments, mean (95% CrI) differences vs placebo/vehicle were –10.40 (–13.44 to –7.41), –8.21 (–10.33 to –6.13), and –6.62 (–8.27 to –4.95), respectively (Figure 3B). Posterior ranks (95% CrI) were 1.17 (1–2), 2.11 (1–3), and 3.32 (2–5), respectively (Figure 4B) (Appendix S18). SUCRA values were 98%, 90%, and 79%, respectively (Figure 5B).

Noninflammatory Lesions Reduction

Across 46 RCTs reporting NILs reduction (Appendix S17), 43 were multicenter studies and 27 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2C), and the number of patients ranged from 107 to 2,813 per study. The top 3 treatments for NILs reduction were: (1) TOA3; (2) topical triple-agent FDC gel; and (3) TFDCRB2. For these 3 treatments, mean (95% CrI) differences vs placebo/vehicle were –17.74 (–22.56 to –12.85), –13.41 (–16.69 to –10.32), and –9.79 (–11.97 to –7.65), respectively (Figure 3C). Posterior ranks (95% CrI) were 1.08 (1–2), 1.96 (1–3), and 3.34 (3–5), respectively (Figure

4C) (Appendix S18). SUCRA values were 99%, 91%, and 79%, respectively (Figure 5C).

Inconsistency and Bias-adjustment Model

The UME model demonstrated no meaningful differences between estimates of RSFC consistency and inconsistency models (Appendix S19). There were no meaningful differences in estimates of RSFC and bias adjustment models (Appendix S20), indicating the robustness of estimates in base-case models.

Threshold Analysis

Threshold analysis for all 3 efficacy outcomes indicated that, in most instances, uncertainty surrounding results (illustrated by 95% CrI) was contained within the range where efficacy estimates were expected to remain consistent (Appendix S21). This supported the robustness and stability of the results of the efficacy analyses and treatment rankings, as most of the observed data fell within the predetermined acceptable range for decision-making. Threshold analysis highlighted that the decision was sensitive to bias adjustments for treatment success in only 2 studies[35,36] and for ILs reduction in only 4 studies.[37-40] Threshold analysis also demonstrated robustness to bias adjustments in most of the studies with wide, invariant intervals.

Safety and Tolerability

SLR showed that the topical triple-agent FDC gel was tolerated well (Appendix S22), with low rates of discontinuation due to treatment-emergent adverse events (2.8%). Double-agent FDCs had a higher proportion of patients with treatment-related adverse events (nearly 32%). Topical triple-agent FDC gel had a better safety and tolerability profile with lower burning (4.4%) and stinging cases (2.1%) than topical double-agent FDC (adapalene/BPO) FDC, which had a greater incidence of burning (5.5%) and stinging (4.1%). Furthermore, no scaling, itching, and erythema were reported in patients applying topical triple-agent FDC gel. Although combinations of topical double-agent FDCs with oral antibiotics had less frequent adverse events (26.3%), the side effects were more systemic in nature.

DISCUSSION

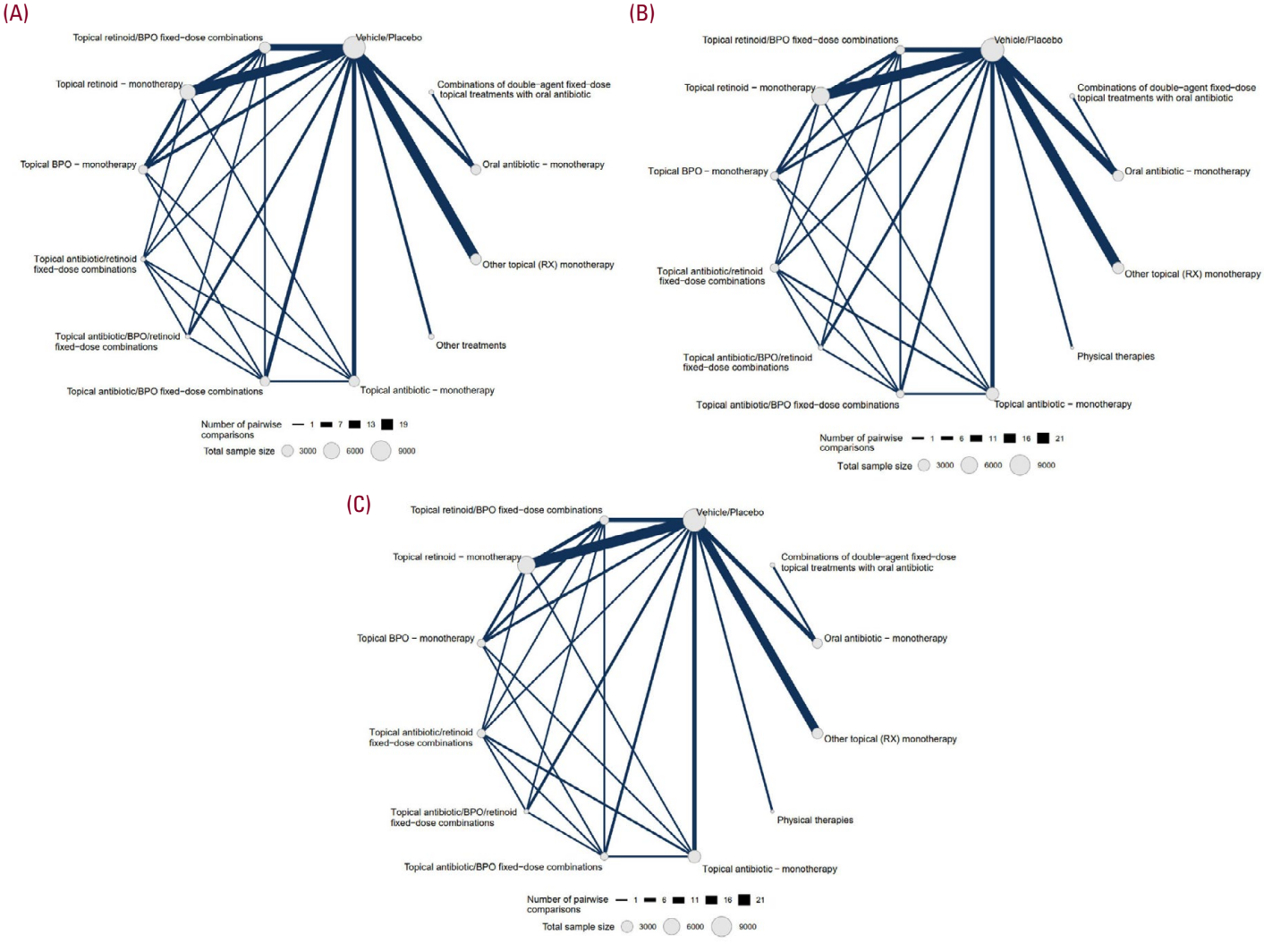
Our analysis showed that for treatment success outcomes, topical triple-agent FDC gel was superior to all treatments. TOA3 was numerically superior to topical triple-agent FDC gel in reducing ILs and NILs. There was a 90% or greater likelihood that topical triple-agent FDC gel was the most efficacious treatment for each outcome. Collectively, these findings suggest that adding an oral antibiotic to topical double-agent FDC gel does not offer significant benefits compared with topical triple-agent FDC gel. The use of the topical triple-agent FDC gel makes it possible to reduce the need for oral antibiotics, thereby minimizing the risk of antibiotic resistance.[41]

Oral antibiotics, topical antibiotics, topical retinoids, and topical BPO as monotherapies had similar efficacy in reducing ILs. Oral antibiotics as monotherapy appeared efficacious compared with topical monotherapies in reducing ILs. However, topical retinoids demonstrated significantly greater efficacy for NILs, while oral antibiotics alone were deemed inadequate. Topical and oral antibiotics were less efficacious than other topical monotherapies, while oral contraceptives were comparable to topical double-agent FDC for treatment success outcomes. Overall, monotherapies of oral antibiotic or topical treatments ranked lower than combined treatments in terms of efficacy. Physical therapies appeared more successful in reducing ILs compared with NILs.

Across all outcomes, an oral antibiotic was more efficacious when given with topical treatment rather than as monotherapy; but adding an oral antibiotic to topical therapy introduces safety and tolerability concerns. Our SLR found that when treatments are combined, major adverse events are generally due to the oral antibiotic, not the topical therapy. Systemic antibiotics for the treatment of moderate-to-severe acne, such as tetracyclines or macrolides, have contraindications, adverse events, and the potential for increased antibiotic resistance.[5-8] These adverse consequences are bypassed when the antibiotic is administered topically. The anti-inflammatory properties of topical clindamycin can also provide a moderating effect on the cutaneous safety and tolerability of adapalene and BPO,[42] which may explain why our SLR found a lower incidence of adverse events/tolerability issues such as burning and stinging for topical triple-agent FDC gel compared with double-agent FDC gel. The efficacy and safety of topical triple-agent FDC gel may also be attributed to a polymeric gel formulation of the vehicle that provides a uniform distribution of ingredients, a combination of active ingredients, or both.[42]

Shi et al reported that combining topical retinoids with BPO was the best option, followed by topical antibiotics and BPO, for mild-to-moderate acne.[11] Stuart et al found that adapalene with BPO was the most efficacious for mild-to-moderate acne;[10] but their study did not consider several treatments, such as tazarotene, trifarotene, and clascoterone. Mavranezouli et al measured efficacy based on the percentage change in total lesion counts for moderate-to-severe acne.[43] Consistent with our findings, that study demonstrated that topical FDCs and combinations of oral antibiotics with topical double-agent FDC are efficacious for moderate-to-severe acne. Also in line with our findings, Huang et al concluded that topical triple-agent FDC gel and TOA3 were efficacious, but they did not focus on moderate-to-severe acne and they included only pharmacological treatments.[12] That study also used the frequentist method, whereas our study used the more robust Bayesian framework. Both Huang et al and Mavranezouli et al found that oral retinoids are the most efficacious treatment for reducing ILs and NILs.

FIGURE 2. Network plots of included studies. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.



The width of each line connecting 2 treatments (nodes) is proportional to the number of head-to-head studies for that comparison.
BPO, benzoyl peroxide.

Oral isotretinoin is efficacious for severe acne with scarring,[44] but its adverse event profile and teratogenicity require specially trained prescribers and close monitoring.[5-8] No RCTs of oral retinoids met the inclusion criteria for our study, which included RCTs published through February 2023 with both quantitative and qualitative clinician assessments of efficacy, per the FDA guidance.[15] We also included studies of both pharmacological and non-pharmacological treatments for the treatment of moderate-to-severe facial acne.

A primary advantage of our study was the study-level threshold analysis for all 3 outcomes, representing an approach that had not been explored previously in the field. We also conducted an end-to-end feasibility analysis of the depth and rigor of our research. The NMA included a broad range of acne treatments and a larger number of RCTs, which is expected to bring significant heterogeneity. We conducted a comprehensive feasibility assessment to identify variability in trial and baseline characteristics within and between treatment groups. We

FIGURE 3. League tables for indirect pairwise comparisons. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin; log-odds ratios (95% CrI). (B) Absolute change in inflammatory lesions; mean (95% CrI) differences. (C) Absolute change in noninflammatory lesions; mean (95% CrI) differences.

(A)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Other treatments	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic- monotherapy	**0.67 (0.29, 1.05)**										
Other treatments	**1.28 (0.79, 1.79)**	**0.61 (0.01, 1.30)**									
Topical antibiotic/BPO fixed-dose combinations	**1.27 (0.95, 1.59)**	**0.60 (0.13, 1.13)**	-0.01 (-0.62, 0.58)								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**1.84 (1.36, 2.29)**	**1.17 (0.57, 1.77)**	0.56 (-0.18, 1.24)	**0.57 (0.03, 1.05)**							
Topical antibiotic/retinoid fixed-dose combinations	**1.23 (0.77, 1.71)**	0.56 (-0.04, 1.18)	-0.05 (-0.74, 0.62)	-0.04 (-0.54, 0.47)	**-0.61 (-1.17, -0.03)**						
Topical retinoid/BPO fixed-dose combinations	**1.36 (1.12, 1.58)**	**0.69 (0.25, 1.12)**	0.08 (-0.48, 0.63)	0.08 (-0.29, 0.45)	-0.49 (-0.98, 0.04)	0.13 (-0.38, 0.64)					
Topical antibiotic- monotherapy	**0.64 (0.32, 0.95)**	-0.02 (-0.51, 0.48)	**-0.64 (-1.22, -0.05)**	**-0.63 (-1.01, -0.25)**	**-1.20 (-1.71, -0.66)**	**-0.58 (-1.11, -0.09)**	**-0.71 (-1.08, -0.33)**				
Topical BPO - monotherapy	**0.73 (0.43, 1.05)**	0.06 (-0.42, 0.54)	-0.55 (-1.17, 0.05)	**-0.54 (-0.92, -0.14)**	**-1.11 (-1.63, -0.58)**	**-0.50 (-0.88, -0.11)**	**-0.62 (-0.99, -0.31)**	0.09 (-0.32, 0.49)			
Other topical (RX) monotherapy	**0.85 (0.56, 1.17)**	0.18 (-0.29, 0.68)	-0.43 (-1.01, 0.15)	-0.42 (-0.87, 0.05)	**-0.99 (-1.54, -0.38)**	-0.38 (-0.95, 0.21)	**-0.50 (-0.88, -0.11)**	0.21 (-0.24, 0.67)	0.12 (-0.33, 0.56)		
Topical retinoid - monotherapy	**0.74 (0.53, 0.93)**	0.07 (-0.34, 0.48)	**-0.54 (-1.11, -0.01)**	**-0.53 (-0.89, -0.19)**	**-1.10 (-1.57, -0.58)**	**-0.49 (-0.98, -0.04)**	**-0.62 (-0.88, -0.34)**	0.10 (-0.28, 0.44)	0.01 (-0.33, 0.34)	-0.11 (-0.49, 0.26)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**1.69 (1.01, 2.82)**	**1.02 (0.46, 1.54)**	0.41 (-0.42, 1.22)	0.42 (-0.26, 1.15)	-0.15 (-0.97, 0.65)	0.46 (-0.35, 1.30)	0.34 (-0.33, 1.02)	**1.05 (0.26, 1.79)**	**0.96 (0.24, 1.67)**	**0.84 (0.10, 1.56)**	**0.95 (0.26, 1.63)**

(B)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Physical therapies	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic - monotherapy	**-3.71 (-5.09, -2.39)**										
Physical therapies	-4.67 (-10.1, 0.95)	-0.96 (-6.59, 4.76)									
Topical antibiotic/BPO fixed-dose combinations	**-6.62 (-8.27, -4.95)**	**-2.91 (-5.11, -0.78)**	-1.95 (-7.68, 3.83)								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**-8.21 (-10.33, -6.13)**	**-4.50 (-7.00, -2.05)**	-3.55 (-9.32, 2.03)	-1.60 (-4.22, 0.87)							
Topical antibiotic/retinoid fixed-dose combinations	**-5.08 (-6.54, -3.64)**	-1.37 (-3.35, 0.57)	-0.41 (-6.12, 5.23)	1.54 (-0.57, 3.63)	**3.13 (0.70, 5.66)**						
Topical retinoid/BPO fixed-dose combinations	**-5.34 (-6.67, -4.06)**	-1.63 (-3.54, 0.19)	-0.67 (-6.31, 4.82)	1.26 (-0.74, 3.21)	**2.87 (0.53, 5.20)**	-0.26 (-2.16, 1.57)					
Topical antibiotic - monotherapy	**-3.27 (-4.41, -2.19)**	0.44 (-1.33, 2.13)	1.40 (-4.39, 6.91)	**3.34 (1.47, 5.18)**	**4.94 (2.64, 7.25)**	**1.81 (0.37, 3.30)**	**2.07 (0.50, 3.77)**				
Topical BPO - monotherapy	**-3.63 (-5.10, -2.17)**	0.09 (-1.90, 2.07)	1.04 (-4.76, 6.65)	**2.99 (1.02, 4.96)**	**4.59 (2.02, 7.20)**	1.45 (-0.48, 3.48)	**1.72 (0.01, 3.52)**	-0.35 (-2.05, 1.39)			
Other topical (RX) monotherapy	**-3.59 (-4.69, -2.53)**	0.12 (-1.62, 1.76)	1.06 (-4.65, 6.65)	**3.03 (1.06, 4.99)**	**4.63 (2.29, 7.00)**	1.49 (-0.32, 3.22)	**1.76 (0.10, 3.56)**	-0.31 (-1.84, 1.23)	0.04 (-1.77, 1.84)		
Topical retinoid - monotherapy	**-3.39 (-4.06, -2.74)**	0.32 (-1.20, 1.82)	1.28 (-4.27, 6.79)	**3.23 (1.41, 4.94)**	**4.82 (2.65, 7.06)**	**1.69 (0.21, 3.23)**	**1.95 (0.63, 3.30)**	-0.12 (-1.34, 1.07)	0.23 (-1.26, 1.70)	0.19 (-1.06, 1.41)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**-10.40 (-13.44, -7.41)**	**-6.69 (-9.42, -3.96)**	-5.73 (-12.06, 0.38)	**-3.78 (-7.32, -0.42)**	-2.18 (-5.87, 1.45)	**-5.32 (-8.67, -2.04)**	**-5.06 (-8.32, -1.72)**	**-7.12 (-10.42, -3.96)**	**-6.77 (-10.13, -3.41)**	**-6.81 (-10.00, -3.65)**	**-7.01 (-10.14, -3.97)**

(C)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Physical therapies	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic - monotherapy	**-2.60 (-5.03, -0.08)**										
Physical therapies	0.20 (-5.94, 6.40)	2.85 (-4, 04 9.41)									
Topical antibiotic/BPO fixed-dose combinations	**-8.34 (-11.00, -5.72)**	**-5.73 (-9.40, -2.20)**	**-8.50 (-15.32, -1.95)**								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**-13.41 (-16.69, -10.32)**	**-10.83 (-15.17, -6.71)**	**-13.62 (-20.43, -6.40)**	**-5.10 (-9.01, -1.22)**							
Topical antibiotic/retinoid fixed-dose combinations	**-8.32 (-10.95, -5.76)**	**-5.73 (-9.51, -2.10)**	**-8.50 (-15.02, -2.12)**	0.02 (-3.39, 3.52)	**5.19 (1.22, 9.00)**						
Topical retinoid/BPO fixed-dose combinations	**-9.79 (-11.97, -7.65)**	**-7.22 (-10.51, -3.92)**	**-10.06 (-16.51, -3.50)**	-1.53 (-4.52, 1.89)	3.61 (-0.10, 7.33)	-1.54 (-4.71, 1.69)					
Topical antibiotic - monotherapy	**-3.79 (-5.71, -1.84)**	-1.23 (-4.42, 1.91)	-4.04 (-10.51, 2.46)	**4.52 (1.63, 7.53)**	**9.65 (5.91, 13.25)**	**4.55 (2.04, 7.10)**	**6.00 (3.30, 8.91)**				
Topical BPO - monotherapy	**-4.59 (-7.04, -2.06)**	-2.03 (-5.52, 1.63)	-4.83 (-11.32, 1.71)	**3.73 (0.50, 7.24)**	**8.80 (4.91, 12.86)**	**3.73 (0.52, 7.33)**	**5.24 (2.36, 8.11)**	-0.86 (-3.61, 2.26)			
Other topical (RX) monotherapy	**-5.32 (-7.06, -3.52)**	-2.73 (-5.85, 0.31)	-5.53 (-12.02, 0.91)	3.00 (-0.21, 6.32)	**8.14 (4.62, 11.91)**	3.02 (-0.14, 6.21)	**4.52 (1.71, 7.32)**	-1.54 (-4.12, 1.14)	-0.72 (-3.80, 2.31)		
Topical retinoid - monotherapy	**-7.14 (-8.29, -6.01)**	**-4.53 (-7.32, -1.98)**	**-7.30 (-13.71, -1.12)**	1.23 (-1.63, 4.03)	**6.33 (3.00, 9.70)**	1.24 (-1.51, 3.91)	**2.62 (0.45, 4.90)**	**-3.31 (-5.52, -1.24)**	-2.61 (-5.20, 0.02)	-1.83 (-3.94, 0.39)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**-17.74 (-22.56, -12.85)**	**-15.12 (-19.41, -11.02)**	**-17.92 (-25.71, -9.94)**	**-9.43 (-14.90, -4.00)**	-4.32 (-10.24, 1.46)	**-9.40 (-15.01, -3.92)**	**-7.92 (-13.23, -2.63)**	**-13.93 (-19.32, -8.61)**	**-13.13 (-18.74, -7.71)**	**-12.42 (-17.61, -7.23)**	**-10.62 (-15.71, -5.62)**

Results are presented as row vs column. Values in cells represent estimated log-odds ratios and mean differences with their 95% credible intervals (95% CrI). All values in bold are statistically significant at the 0.05 significant level.

FIGURE 4. Posterior rank analysis. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.

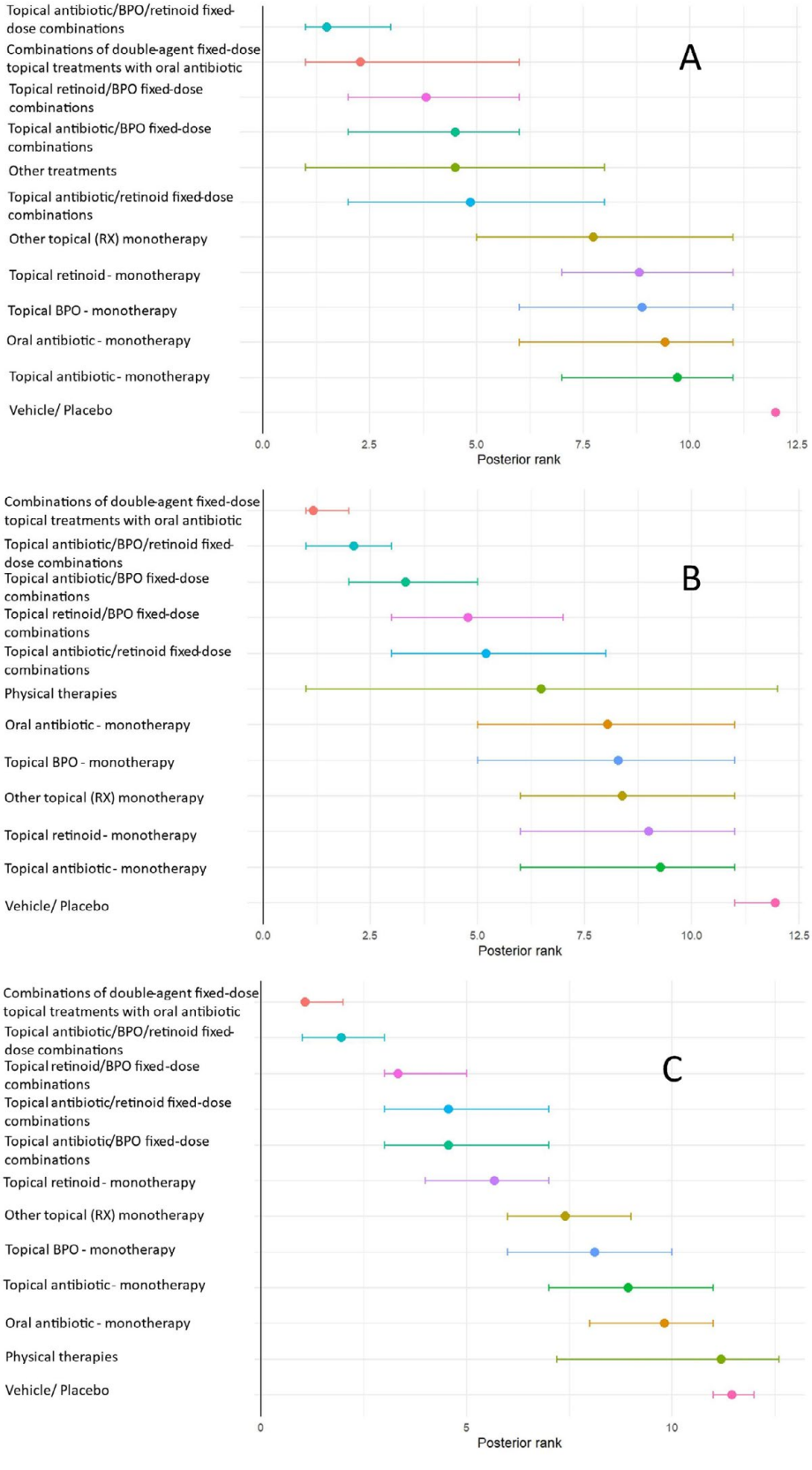


FIGURE 5. Surface under cumulative ranking plots. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.

conducted meta-regression to identify potential treatment effect modifiers, which we then used to select covariates in the NMA. We also used class models to improve the precision of treatment effects and connect previously unconnected networks, expanding the evidence base.

Limitations

Our study excluded articles in languages other than English, but this has not been shown to bias the results of SLR/NMA.[45] Due to the limited number of studies available, we were unable to analyze specific dosing schedules or formulations separately. During the feasibility assessment, we observed that the proportion of patients with moderate acne might influence treatment outcomes, but 31% of studies did not report this proportion at baseline. Thus, we could not perform network meta-regression to account for this potential effect modifier. Differences in study characteristics and geographical locations might have acted as effect modifiers, introducing heterogeneity into the analysis. Results for some treatments were based on limited evidence and network connections. Nevertheless, a study-level threshold analysis demonstrated the robustness of the NMA results against all influences from study bias and sampling variation.

CONCLUSION

In conclusion, this NMA synthesized data from a wide range of treatments for moderate-to-severe acne vulgaris. Topical triple-agent FDC gel was the most efficacious treatment based on the treatment success outcome, surpassing both topical/oral monotherapies and topical double-agent fixed-dose combinations.

DISCLOSURES

AAD was an employee and stakeholder at Bausch Health US LLC at the time of the study. TL is an employee and stockholder at Ortho Dermatologics. ARC, BG, DD, DR, HB, JCH, JKLT, MSA, SB, SKD, and SPC have received consulting fees from Bausch Health US, LLC. GJ was an employee of Bausch Health US, LLC when the study was conducted and may hold stock in Bausch Health. JCH is an advisor, investigator, and speaker for Bausch Health US, LLC. HB is an advisor, investigator, and speaker for Bausch Health US, LLC and Galderma; investigator, and speaker for Almirall US, LLC; investigator for Sol Gel Technologies Ltd.; advisor, speaker for Sun Pharma; and speaker for Novan, Inc. JKLT is a consultant, advisor, speaker, honoraria for Bausch Health US, LLC, Cutera, Inc, Galderma, L'Oreal, and Walgreens Boots Alliance.

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ORIGINAL ARTICLE

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A Practical Algorithm Integrating Skin Care With Nonenergy and Injectable Dermatologic Procedures to Improve Patient Outcomes and Satisfaction

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ABSTRACT

Background: The most rapidly increasing medical aesthetic procedures for facial antiaging comprise nonenergy and injectable treatments. Currently, standards for skin care before, during, and after nonenergy and injectable treatments are lacking. The algorithm on supportive skin care for facial antiaging nonenergy and injectable treatments aims to stimulate healing, reduce downtime, and improve comfort and treatment outcomes.

Methods: A panel of 7 global physicians employed a modified Delphi method and reached a consensus on an algorithm for supportive skin care for nonenergy and injectable antiaging treatments based on the best available evidence and the panel members' clinical experiences and opinions.

Results: The algorithm has a pretreatment (starts 2 – 4 weeks before the procedure) and treatment or ongoing (day of treatment) section, followed by care after the procedure (0 – 7 days) and follow-up care (1 – 4 weeks after the procedure). Applying a broad-spectrum sunscreen with an SPF 30 or higher, combined with protective measures, such as wearing a wide-brimmed hat and sunglasses, is recommended to protect the face from sun exposure. Dyschromia is a significant concern for those with richly pigmented skin. Clinicians may recommend skin care using a gentle cleanser and moisturizer containing vitamins C and E, retinoid, or other ingredients, such as niacinamide, kojic acid, licorice root extract, azelaic acid, and tranexamic acid, depending on the patient's facial skin condition.

Conclusion: Nonenergy and injectable procedures combined with skin care or topical treatments may improve outcomes and patient satisfaction. Topical antioxidants and free radical quenchers can combat photodamage and may offer a safe alternative to topical hydroquinone.

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INTRODUCTION

Medical aesthetic procedures for facial antiaging treatment using nonenergy and injectable treatments are rapidly increasing.[1,2] The American Society for Aesthetic Plastic Surgery (ASAPS) reported that in 2021 over 1 billion dollars were spent on injectables.[1] Together, botulinum toxin and hyaluronic acid injectable procedures comprised the top two non-surgical treatments performed in 2021, with botulinum toxin as the number one medical aesthetic procedure.[1] The injection-based device segment is projected to grow continuously by over 10% annually between 2022 and 2027 by many market research groups. Specifically, Fortune Business Insights shared that the global medical aesthetics market shows that the nonenergy-based segment is the largest portion of the global aesthetic market.[3] Many publications have addressed methods to reduce adverse events related to nonenergy and injectable treatments; however, few algorithms exist on skincare measures before, during, and after nonenergy and injectable treatments.[4,5] Currently, standards for skin care before, during, and after medical aesthetic procedures are lacking.[4,5] As a result, skin care use for managing conditions

associated with nonenergy and injectable treatments is highly variable.[4,5] Nonenergy device-based treatments may improve skin conditions by inducing cutaneous changes that remodel the skin matrix.[6-11] Adverse events may occur, prolonging the duration and severity of the healing process.[4-7]

The current algorithm aims to provide clinicians with skin care recommendations when treating patients with nonenergy-based and injectable treatments for facial antiaging to stimulate healing, reduce downtime, and improve comfort and treatment outcomes.

MATERIALS AND METHODS

A panel of 7 global physicians (panel) who perform medical aesthetic procedures convened a face-to-face meeting and online follow-up to develop and customize the algorithm. The panel found this resource can provide the following: Insight into the fascinating similar philosophies across continents, which may reduce practice variability, a review of the peri/post procedure space, education for patients with richly pigmented skin, and highlighted differences within the injectable space. The panel employed a modified Delphi method and reached a consensus on the algorithm for periprocedural skin care for nonenergy and injectable antiaging treatments based on the best available evidence and the panel members' clinical experiences and opinions.[12,13]

Literature Searches

Structured literature searches on PubMed and Google Scholar (secondary source) by a physician (TE) and a physician/scientist (AA) were conducted from December 20 to 22, 2022, for publications in the English language from 2010 to January 2023. The following terms were used for the literature searches.

Group 1: Aesthetic dermatology AND nonenergy facial treatment; OR fillers OR injectables OR chemical peels AND hyperpigmentation OR post-inflammatory hypopigmentation.
Group 2: Aesthetic dermatology; pre-/post-procedure measures AND skincare; OR skincare for nonenergy aesthetic facial treatments; OR skincare for injectable treatment OR skincare for chemical peels

The searchers reviewed the titles and abstracts and then the full articles. Excluded were duplicates and poor-quality studies. In case of a review or update, we used the latest version. The reviewers selected 54 nonenergy and injectable treatment articles; after excluding 24 articles, 30 remained. Article types included were clinical studies, algorithms, consensus papers, guidelines, meta-analyses, systematic reviews, and review papers (Figure 1).

Each selected clinical publication that included periprocedural skin care or skin care combined with nonenergy and injectable treatment was graded based on reviewer consensus.[12] The reviewers assigned a level of evidence for each treatment (levels A, B, C, and 1 to 4) using the pre-established criteria.[12] No grading was done due to a lack of clinical studies on periprocedural skin care.

Development of the Algorithm

Based on the literature results and in-field practice, the global panel worked in small groups on implementing and revising the initial algorithm skeleton proposed by TL and AA. The global panel reconvened into a plenary group to reach a consensus through blinded reiterations. Reviewing, editing, customizing the final algorithm, obtaining consensus, and discussing and reviewing this manuscript took place online.

The Algorithm

The purpose of a clinical algorithm is to guide medical decision-making by standardizing treatment regimens to encourage compliance with evidence-based recommendations.[4,5] The algorithm on supportive skin care for nonenergy and injectable treatments has a pretreatment (starts 2 – 4 weeks before the procedure) and treatment (day of treatment) section, followed by care after the procedure (0 – 7 days) and follow-up care (1 – 4 weeks after the procedure or ongoing) (Figure 2). Nonenergy facial and injectable treatments included microdermabrasion, micro-needling, threads, chemical peels, fillers, and neuromodulator injections. Although microdermabrasion and micro-needling may use an energy-based device, the treatment is minimally invasive and, therefore, fits in the category. Moreover, these procedures are frequently combined with skin care or topical treatments, which is relevant for the algorithm.

Medical and Dermatological History

Pre-procedural consultation includes clarifying individual patient goals and expectations of the treatment, followed by a treatment plan.

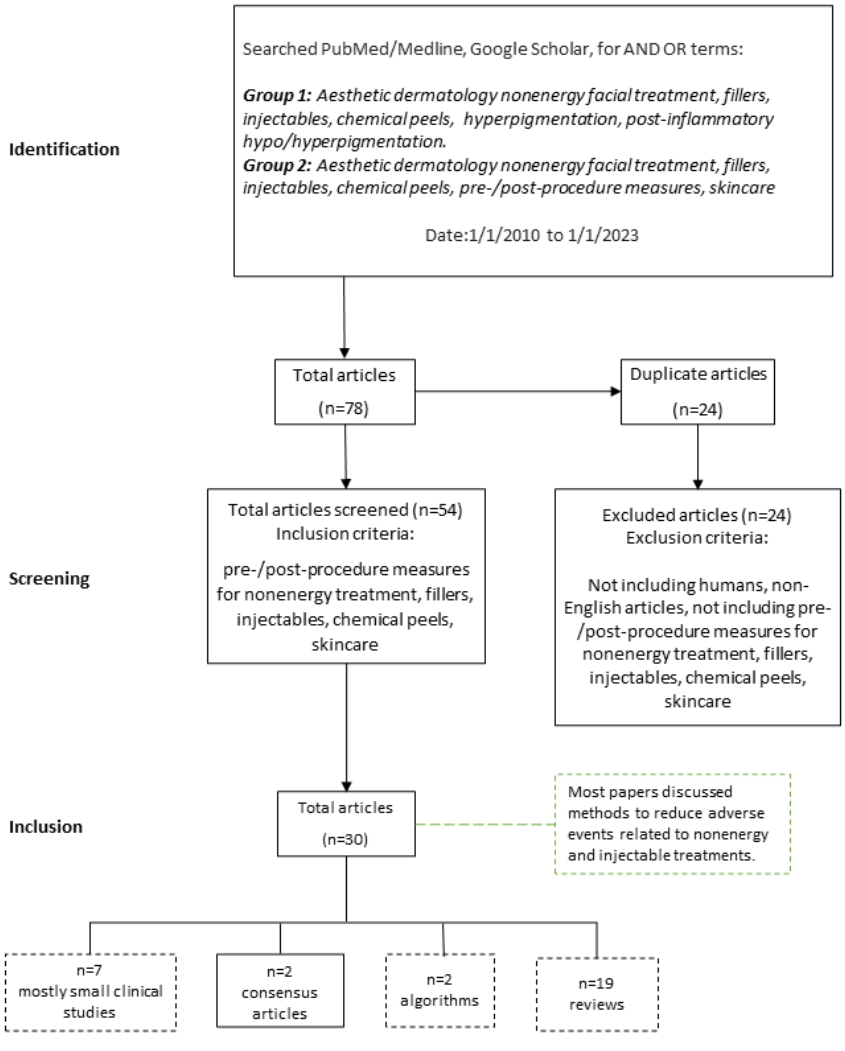
Outcomes of previous skin treatments should be discussed with the patient, especially responses to dermabrasion or chemical peels.[4,5,14]

Before recommending nonenergy-based and injectable treatments, the medical and dermatological history of the patient is to be obtained with specific attention to skin issues that the procedure may exacerbate, such as history, ethnicity, and/or Fitzpatrick or Roscea skin type, that may predict a higher risk for pigmentary or scarring complications.[4,5,14]

Pretreatment Measures

Starting 2 to 4 weeks before the procedure, clinicians advise patients to avoid excessive sun exposure before, during, and after facial nonenergy-based and injectable treatments.[4,5,14,15] To protect the face from sun exposure, applying a broad-spectrum

FIGURE 1. Structured literature search results.



[1]Excluded: Poor-quality studies. In case of a review or update, the latest version was used.
Due to a lack of clinical studies on periprocedural measures and skin care, no grading was done.

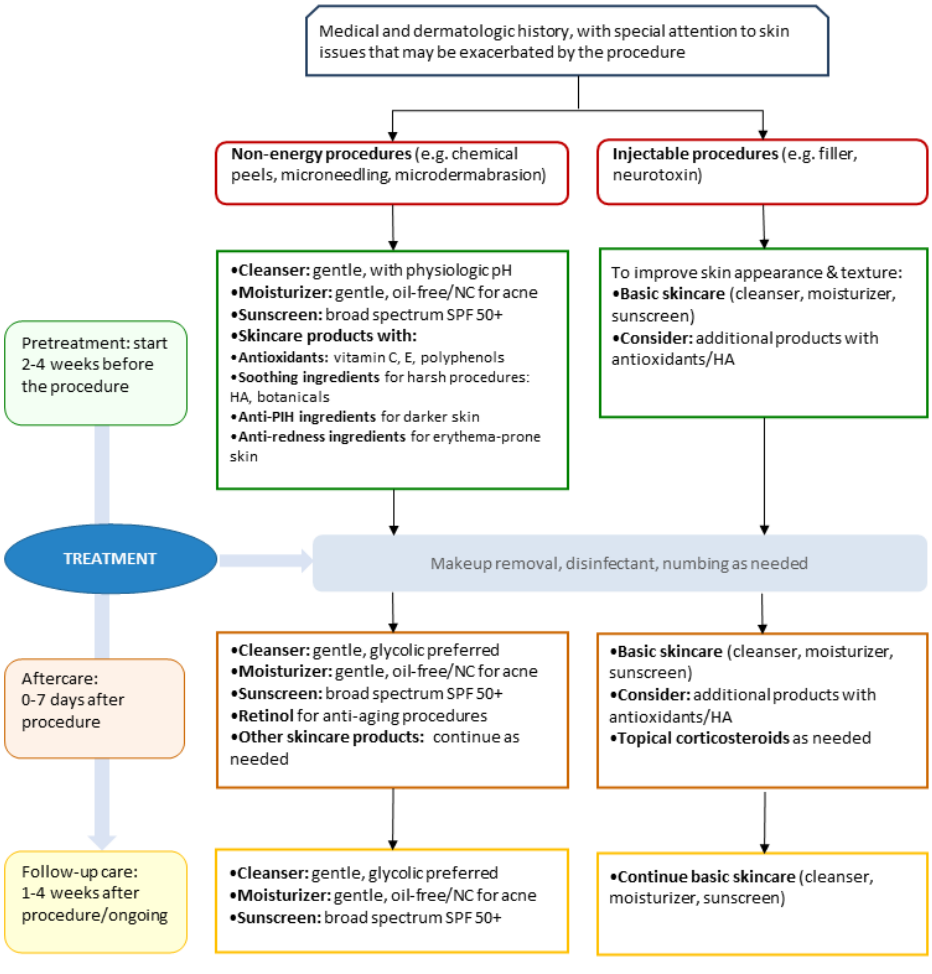
sunscreen with an SPF 50 or higher, combined with protective measures, such as wearing a wide-brimmed hat and sunglasses, is recommended.[4,5,14,15]

Tinted iron oxide sunscreens without a white cast in richly pigmented skin could improve compliance. In addition, using topical technologies that contain ingredients with antioxidants and free radical quenchers may help to prevent dyschromia,[14-16] which is a significant concern for those with richly pigmented skin and of Asian descent.[14-17]

Injecting fillers sub-dermally with longer, slower injection times may help decrease the risk of dyschromia.[17,18] Healthcare providers should be informed on skin thickness variability among facial areas in richly pigmented patients, which affects optimal injection depth.[17,18] During the procedure, skin cleansing products are addressed, along with judicious techniques to minimize unintended cutaneous injury or inflammation.

Clinicians may pretreat patients with products to prevent hyper or hypopigmentation before nonenergy or injectable treatments. However, this recommendation is primarily for patients with richly pigmented skin or those with a history of dyschromia or abnormal scarring.[4,5,14-17] Melanocytes are hyper-reactive in richly pigmented skin, leading to more pigment disorders, such as hyper or hypopigmentation, a frequent sequela of inflammatory dermatoses, skin injury, or photodamage.[14-17] Pretreatment prevention of hyper or hypopigmentation comprises topical arnica/bromelain or hydroquinone and agents to impact melanogenesis.[4,5,14,15] Other options are products containing niacinamide, kojic acid (KA), azelaic acid (AzA), retinoids, and tranexamic acid (TXA). Pretreatment with skin care using a

FIGURE 2. Algorithm on integrative skin care for facial nonenergy and injectable dermatologic procedures.



HA = hyaluronic acid; NC = noncomedogenic; HSV = herpes simplex virus

gentle cleanser and moisturizer containing a retinoid or other ingredients, such as vitamin C, niacinamide, KA, licorice root extract, AzA, and TXA, is frequently recommended depending on the patient's facial skin condition.[4,5,14-17] These products may impact melanogenesis or melanosome transfer, while others enhance melanosome degradation.[15]

Measures During the Treatment Phase

Before nonenergy-based and injectable treatments, avoid drying alcohol, retinol peels, and agents such as acetylsalicylic acid, high-dose vitamin E and omega 3, ginkgo biloba, and garlic that can enhance the risk of bleeding and or bruising, and non-steroidal anti-inflammatory drugs (NSAIDs), amongst other agents, is recommended.[4,5,14,15] The panel agreed that depending on the depth of the peel, avoiding them for at least two weeks or longer prior to the procedure is recommended, together with avoiding unprotected sun exposure.

Before injectable treatments, the patient's skin should be clean so makeup or other material does not cover or camouflage, for example, blood vessels. Facial makeup must be fully removed, and the skin should be cleansed with a gentle facial cleanser. Upon performing the procedure, typically, an antimicrobial solution is applied to the treatment area.[4,5,14] Agents such as isopropyl alcohol, chlorhexidine, or hypochlorous acid (HOCl) are frequently applied for skin preparation.[4,5] Isopropyl alcohol, although inexpensive, can irritate the skin and is flammable, whereas chlorhexidine, although effective, has ocular and ototoxicity.[4,5,15,19,20] Stabilized HOCl for skin preparation before and after nonenergy or injectable treatments is highly active against bacterial, viral, and fungal microorganisms.[21,22] When choosing topical antiseptics, antimicrobial resistance should be taken into account, and factors such as geographic region/practice setting (outpatient versus hospital-based) associated with microbial epidemiology.[4,5]

Aftercare

Aftercare is started immediately after the procedure for up to 7 days. The treatment of pain and anesthesia for nonenergy and injectable procedures should be at the treating physician's discretion and is dependent on the patient and the type of treatment administered.[4,5]

Immediately, post-procedural sunscreen and gentle skin care that may include skin-lightening agents or formulations designed to prevent infection and promote optimum healing are advised.

It is recommended that patients use a gentle facial noncomedonal cleanser typically free of comedonal oils with neutral skin surface physiological pH (4 – 6); formulas with glycolic or lactic acid for skin rejuvenation are recommended.[4,5,15] Patients should continue applying a broad spectrum SPF >50 or more sunscreen as before the procedure and a moisturizer, and consider additional products with antioxidants, HA, or both.[4,5,15] Topical retinol is recommended for those who received drug-based procedures, and other skincare products that were used before the procedure may be continued as needed.

Follow-up care

Follow-up care is provided 1 to 4 weeks after the procedure and comprises skin care as described for aftercare.[4,5,15] The panel agrees that prescribing a skincare routine to patients receiving neuromodulator and dermal filler procedures improves skin quality and overall aesthetic outcomes. The synergy between skin care and injectable procedures improves patient satisfaction and promotes long-term prevention and maintenance. The panel agreed that recommending postprocedure skincare routines long term, beyond 1 to 4 weeks postprocedure, improves outcomes.

Adverse Events

The panel agreed that general neuromodulator and dermal filler procedures do not pose a significant risk of hyper- and hypopigmentation with dyschromia even in more richly pigmented individuals, unlike peels, microdermabrasion, or laser procedures. Delayed adverse effects after various types of filler injections may include pigment change, nodule formation, and infection.[4,5,14-18] Different patterns of pigment change provide clues for etiology and treatment.[15-18] The most common type of pigment change, hyper- and hypopigmentation with dyschromia results from skin trauma.[15-18] Hyper- and hypopigmentation with dyschromia may spontaneously resolve over months, but the diligent use of sunscreen, skin-lightening agents, and possibly superficial chemical peels may hasten resolution.[15] Reticulated brown-red discoloration can occur a few months later at the site of HA fillers, representing a hypersensitivity reaction to the HA filler.[23,24] These pigment changes are unresponsive to hydroquinone and may require laser treatment with Nd:YAG 1064 nm. This brown-red hyper- and hypopigmentation with dyschromia may also respond to hyaluronidase treatment, which dissolves the hyaluronic acid.[23,24] This type of hypersensitivity reaction has not been seen with fillers composed of hydroxyapatite or poly-L-lactic acid.[24]

DISCUSSION

Integrating Skin Care for Facial Nonenergy and Injectable Treatments

Patients frequently choose facial nonenergy or injectable treatments due to the minimally invasive nature, reduced risks, and shortened downtime compared to ablative laser and surgical modalities.[6-11] Cost, age, and access all play a role in the type of treatment considered.

Copious recommendations and publications exist for integrated skin care for energy-based device treatments.[25] The panel agreed that data and recommendations for best practices for periprocedural skin care or skin care combined with aesthetic nonenergy and injectable procedures are relatively limited. For the algorithm on integrated skin care for nonenergy and injectable procedures, we reviewed periprocedural skin care and specific ingredients as an adjunct or combined with nonenergy and injectable facial treatments.

Antioxidants

Topical antioxidants can be effective in protecting against and reversing photodamage of the facial skin.[26] Studies have shown that topical vitamins C and E and the mineral selenium may protect against sunburn and discoloration.[26] Certain forms of these antioxidants are stable and active after application to the skin, such as non-esterified, acidic vitamin C, non-esterified vitamin E, and the isomer D-alpha tocopherol.[26]

Topical Retinoid, Topical Hyaluronic Acid

Adjunctive or combined specialized aesthetic skin care may enhance aesthetic procedure outcomes.[26-31] Creams, serums, and gels containing various ingredients such as HA may improve skin hydration and elasticity.[26-31] The use of skin care by individuals receiving neuromodulator injections has reduced the mean volume and depth of facial lines and hyperpigmentation and improved skin smoothness, tone, and color compared with neuromodulator injections alone.[26,27]

A study of 20 volunteers treated with a neuromodulator and HA injections in the cheeks, nasolabial folds, and lips randomized participants to a skincare regimen for 12 weeks in conjunction with injections.[26] Ten volunteers (group 1) received skin care with a cleanser, antioxidant, exfoliator, retinol, and sunscreen. Group 2 (n = 5) received the same skincare regimen plus a series of 6 alpha-hydroxy acid pigment-balancing peels every 2 weeks, and group 3 (n = 5) received skin care with a cleanser, moisturizer, and SPF 50 sunscreen. Group 2 showed the most marked improvement (blinded evaluator Global Aesthetic Improvement Scale [GAIS]).[26] Groups 1 and 2 exhibited markedly improved self-esteem scores.[26]

Topical Hydroquinone, Niacinamide, Kojic Acid, Licorice Root Extract, Azaleic Acid

Neuromodulator injections, a hydroquinone skincare regime, and daily topical retinoids improved signs of photoaging.[26] A further study combined neuromodulator injections for antiaging treatment with skincare containing retinol adenosine and HA, which optimized total treatment outcomes.[28]

Pre-procedure or follow-up care with skin care using topical products containing niacinamide, KA, AzA, and TXA may be recommended.[29] Niacinamide inhibits melanosome transfer to keratinocytes and may be combined with TXA. A randomized, double-blind, vehicle-controlled study showed improvement in irregular facial hyperpigmentation.[30]

KA is a radical oxygen scavenger and inhibits tyrosinase. A study compared a combination of topical KA and glycolic acid with topical hydroquinone 4% and found superior results for the KA and glycolic acid product.[31]

LIMITATIONS

The panelists agreed that standardization for supportive skin care for nonenergy and injectable facial treatments is lacking, and many products are recommended without expert consensus. Clinical studies on skin care for these procedures mostly have a small sample size, but some used biophysical assays to support the findings. The discussion of skin care containing various ingredients supporting outcomes of nonenergy and injectable treatments was mostly limited to studies that combined skin care with these treatments. As data is lacking on combining nonenergy treatments and injectables with topical products containing niacinamide, KA, licorice root extract, AzA, and TXA, the discussion was limited to informing clinicians on the action of these ingredients.

CONCLUSION

The algorithm provides clinicians with skincare recommendations when treating nonenergy-based and injectable facial antiaging treatments to stimulate healing, reduce downtime, and improve comfort and treatment outcomes. A structured literature search was conducted to guide the algorithm's development. Clinical studies suggest that periprocedural skin care may improve outcomes and patient satisfaction with aesthetic procedures. Procedures combined with skin care or topical treatments improved skin condition.

Dyschromia is a significant issue for richly pigmented skin, and the literature suggests that topical antioxidants and free radical quenchers can protect against photodamage. The use of hydroquinone remains controversial, especially given the alternatives currently available.

DISCLOSURES

This work was supported by an unrestricted educational grant from SkinCeuticals International. The authors contributed to the development of the manuscript, reviewed it, and agreed with its content.

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ORIGINAL ARTICLE

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A Silymarin Antioxidant Serum Improves Facial Acne Alone and as Part of a Treatment Regimen

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ABSTRACT

Background: Silymarin is an antioxidant that can protect against free radicals that cause premature signs of aging and oil oxidation that may contribute to breakouts.

Aims: The objective of these studies was to evaluate a silymarin antioxidant serum alone and in combination with a prescription acne treatment regimen in improving facial appearance in blemish-prone skin.

Methods: Two international studies were conducted. A 12-week study in Brazil enrolled 56 subjects to examine the effect of silymarin antioxidant serum on facial acne. Clinical grading on acne lesions, skin tone, clarity, and postinflammatory hyperpigmentation (PIH) were conducted. In addition, consumer self-assessment, analysis for markers of lipid peroxidation, and sebumeter analysis were completed. Another Unites States (US)/German study enrolled 40 subjects who were on topical prescription acne medications to which silymarin antioxidant serum was added. Acne lesion counts, tolerability, and facial appearance assessments were conducted in this study.

Results: The Brazilian study demonstrated a 45% reduction in inflammatory lesions and a 43% reduction in noninflammatory lesions after 12 weeks of silymarin antioxidant serum use. In addition, sebumeter testing showed a 16% reduction in oiliness at week 1. The US/German study showed the benefits of the serum in persons already on prescription acne therapy by reducing facial erythema by 60%, dryness by 49%, and scaling by 67%.

Conclusion: Silymarin is shown in clinical testing to have significant benefits in reducing lipid peroxidation, oiliness, and PIH, and in improving key markers of skin aging. Additionally, the serum can be used alone or as an adjunctive treatment in acne therapy to further benefit aging, acne-prone skin.

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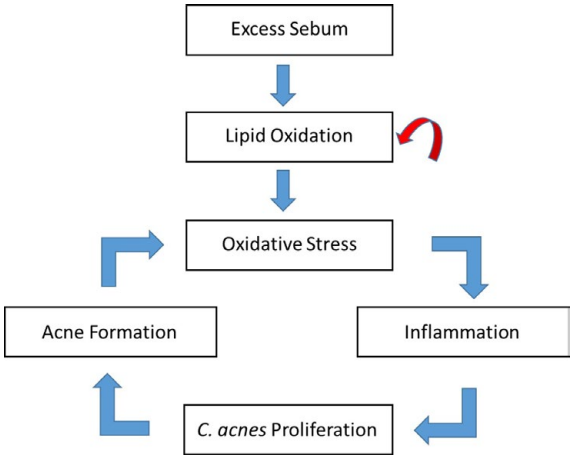
INTRODUCTION

Acne is an inflammatory condition common in adolescents, but blemish-prone skin can persist into adulthood.[1,2] The pathogenesis of acne is characterized by increased sebum production, follicular hyperkeratinization, *C. acnes* colonization, and inflammation, which manifest as inflammatory and noninflammatory acne lesions. Acne is believed to have an underlying genetic component, but it can be influenced by a wide variety of factors including age, gender, ethnicity, hormones, diet, pollution, climate, and stress.[3-7]

A link has been proposed between sebum and acne, with sebum oxidation perhaps contributing to enhanced formation of lesions.[8,9] Acneic skin is reported to have both higher levels of oxidative stress and lower levels of antioxidants than healthy skin.[10] Additional oxidative environmental factors, such as ultraviolet (UV) radiation and pollution, generate free radicals that exacerbate the condition. Oxidative stress, particularly lipid peroxidation, contributes to inflammation, which creates a favorable environment for acne-causing bacteria (Figure 1). It has been proposed that topical antioxidant application can improve this environment and help reduce the prevalence of acne.[11-16]

Silymarin is a standardized extract from the seeds of the milk thistle plant (*Silybum marianum*) which typically contains 70% to 80% of an isomeric mixture of flavonoid complexes called flavonolignans. The main flavonolignans comprising silymarin are silybin, isosilybin, silychristin, dehydrosilybin, and silydianin, in addition to the flavonoid taxifolin. The highest concentration, comprising roughly 50% to 60% of silymarin, is silybin, which is the major bioactive component of the extract. Silymarin is a powerful antioxidant owing to the complimentary free radical scavenging abilities of the various

FIGURE 1. The role of lipid oxidation in the acne cycle and opportunity for antioxidant intervention.



flavonolignan isomers. As such, it is reported to have a range of biological activities, including the ability to help reduce lipid peroxidation.[17-19]

A formula of 0.5% silymarin is combined with 15% L-ascorbic acid and 0.5% ferulic acid to form a triple-antioxidant serum that may provide protection against free radicals that cause both premature signs of aging and oil oxidation that may contribute to acne.[20] The oil-free serum also contains 0.5% salicylic acid, a well-known monographed acne active. A comprehensive efficacy clinical and international tolerance assessment were designed to evaluate the effectiveness of the silymarin antioxidant serum across parameters of aging, as well as acne reduction when used alone and as part of an acne treatment regimen.

MATERIALS AND METHODS

The initial efficacy study was a 12-week, single center, blinded clinical study conducted in Brazil (CIDP Brasil, Rio de Janeiro, Brazil) on 56 male and female subjects aged 18 to 48, with Fitzpatrick skin types ranging from II to V. The enrolled subjects presented with mild-to-moderate acne, lack of clarity, uneven skin tone, and postinflammatory hyperpigmentation or erythema (PIH/PIE). Subjects applied the serum to the face once daily for the duration of the study in conjunction with a mild cleansing bar and sunscreen. Clinical grading, tolerance evaluations, sebumeter measurements, and subject self-assessments were conducted at baseline and weeks 1, 4, 8, and 12. A randomized subset of the panel (N=30) had sebum sampled from the forehead by swabbing at baseline, week 4, and week 12, which was analyzed for lipid content.

In addition, consumer perception was evaluated upon immediate application and after 1, 2, 4, 8, and 12 weeks of use. Perception was measured on a scale of 1 through 9, where 1 was the most negative response and 9 was the most positive response. The results are expressed as a percentage of favorable responses (score ≥ 6).

TABLE 1.

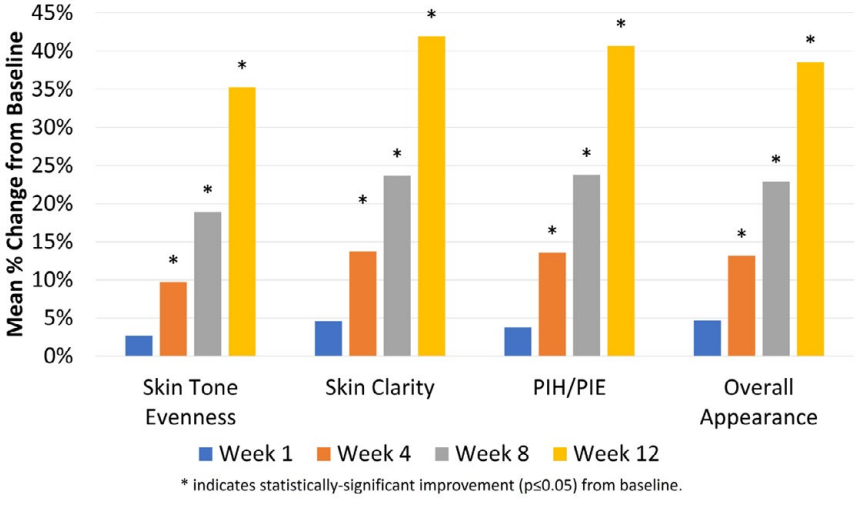
Prescribed Acne Medications
Topical Benzoyl Peroxide
Adapalene
Tretinoin
Tazarotene
Clindamycin
Oral Minocycline

A second international study explored the tolerability of the silymarin antioxidant treatment when used in combination with a variety of prescription acne medications. Forty healthy females aged 18 to 50 of all Fitzpatrick skin types, who were currently using prescription topical acne medications, were enrolled in this international study.[21] Prescribed acne medications are listed in Table 1. To their acne treatment regimen, subjects added a silymarin-containing antioxidant facial serum. The investigators from the United States (Zoe Diana Draelos MD, Dermatology Consulting Services, PLLC, High Point, NC) and Germany (Martina Kerscher MD) rated the subjects for facial dryness, erythema, and edema; while the subjects rated themselves for the facial sensory attributes of stinging, tingling, itching, and burning. All assessments were conducted on a 4-point ordinal scale along with facial photography at baseline and week 4. Subjects also completed a self-assessment questionnaire regarding skin clarity improvement, skin radiance improvement, skin oil presence, and product perception after 1 and 4 weeks of product use.

RESULTS

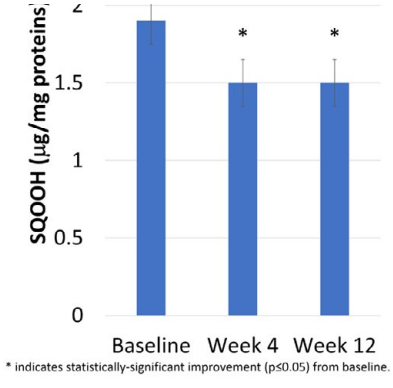
For the efficacy study, 12-week results showed statistically (P<0.001) significant improvement in skin clarity by 42%, PIH by 41%, skin tone evenness by 35%, and overall appearance by 39% after applying the silymarin serum (Figure 2). In addition, sebumeter testing showed a 16% reduction in skin surface oil at week 1 (P<0.001). Furthermore, analysis of the collected sebum samples showed a significant reduction in squalene peroxide at both week 4 and week 12 (Figure 3). Global lesion count showed a modest decreasing trend at week 4, but significant improvement by week 8 and week 12 driven by a reduction in both inflammatory and non-inflammatory lesions. The investigator's global assessment (IGA) of acne severity also showed a significant improvement of 27% at week 12. There was a 45% reduction in inflammatory and a 43% reduction in noninflammatory lesions (Figure 4). Figure 5 illustrates the improvement observed in skin appearance and PIH with the silymarin antioxidant serum. Consumer perception received

FIGURE 2. Bar graph showing the improvement of evaluated skin attributes.



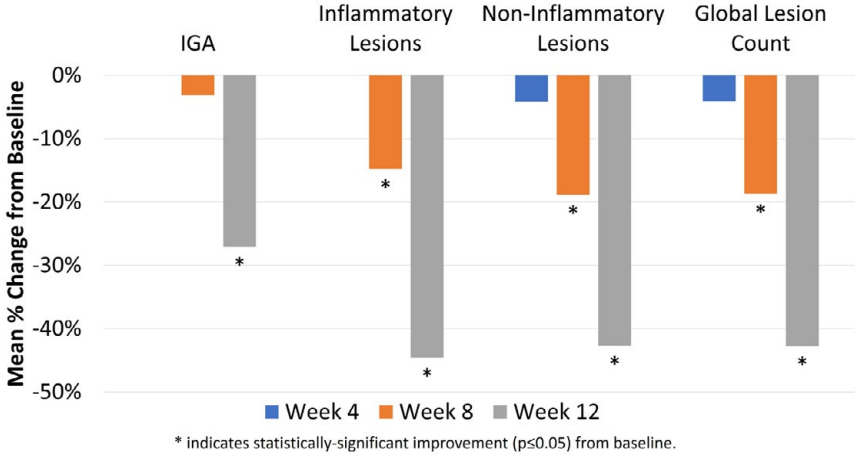
The changes are statistically significant ($P<0.05$).

FIGURE 3. Bar graphs showing sebum peroxidation over time.



Asterisks indicate statistical significance ($P<0.05$).

FIGURE 4. Bar graph showing improvement of evaluated acne parameters. The changes are statistically significant ($P<0.05$).



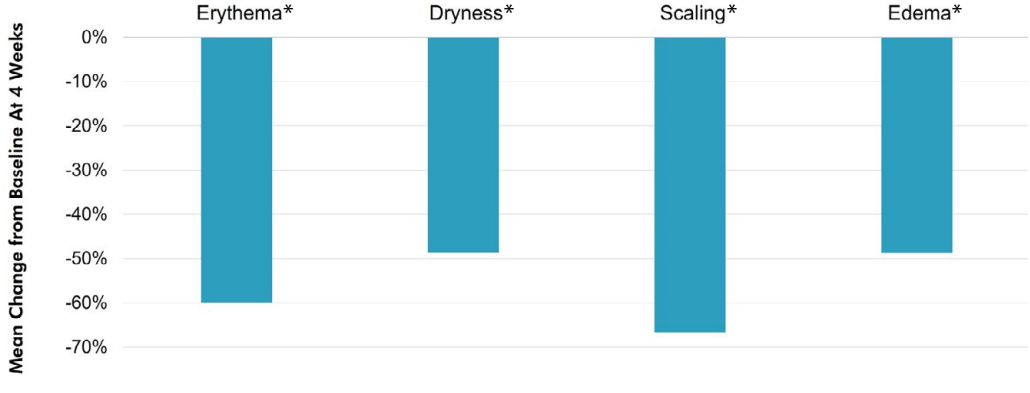
The changes are statistically significant ($P<0.05$).

an overall favorable response (>50% of subjects rating ≥ 6). Additionally, the silymarin antioxidant serum was well-tolerated by the subjects.

In the second international study, after 4 weeks of adding the silymarin antioxidant serum to the subjects' prescribed regimen, the investigator's assessment showed a statistically significant reduction in facial erythema, dryness, and scaling (Figure 6). Additionally, subjects noted a statistically significant reduction in facial tightness and dryness (Figure 7). Photographic visualization also demonstrated facial skin tolerability including erythema, dryness, and scaling (Figure 8). After one week of use, 70% of subjects agreed the serum made their skin feel less oily, 58% felt the serum improved their skin clarity, and 50% felt serum improved skin radiance. Over half the subjects desired to continue using the serum after completion of their prescription acne therapy.

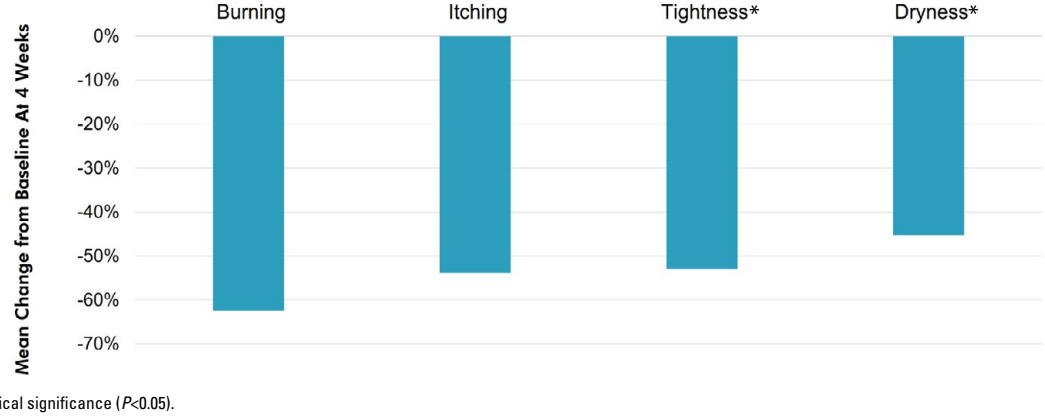
FIGURE 5. Photographic visualization of skin attributes including overall skin appearance, clarity, and postinflammatory hyperpigmentation at various timepoints.

FIGURE 6. Bar graph showing investigator-assessed reductions in key facial symptoms.



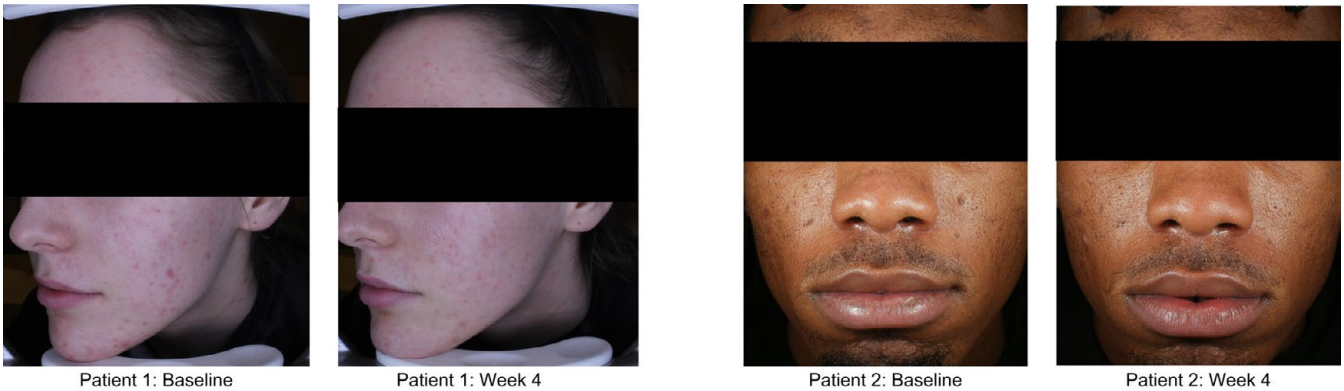
Asterisks indicate statistical significance ($P<0.05$).

FIGURE 7. Bar graph showing subject-assessed reductions in facial sensory attributes.



Asterisks indicate statistical significance ($P<0.05$).

FIGURE 8. Representative photos of facial skin tolerability, including erythema, dryness, and scaling.



Patient 1: Baseline | Patient 1: Week 4 | Patient 2: Baseline | Patient 2: Week 4

DISCUSSION

Acne is a condition with complex etiology. It often persists into adulthood and the incidence in mature women is increasing. There is a need for new topical treatments that address underlying factors that have been associated with the disease. One of the key contributors to the oxidative stress theory of acne is a redox imbalance due to lipid peroxidation within the sebum and progressing through the various stages of comedogenesis. Since antioxidants are well known to help prevent lipid peroxidation, there is an opportunity for topical supplementation to mitigate the disease progression.

The results from the Brazilian study showed that a topical serum containing 0.5% silymarin, 15% vitamin C, 0.5% ferulic acid, and 0.5% salicylic acid was effective in reducing facial acne and improving associated skin attributes such as clarity, tone evenness, and pigmentation. While some skin benefits are seen rather quickly, the strongest improvement in lesional acne is observed with continued usage. This suggests that the fundamental stabilization of lipid peroxidation may be an important underlying strategy for daily management of oily, acne-prone skin while also improving overall skin appearance.

The study demonstrated the fundamental ability of the treatment to broadly decrease the IGA and inflammatory and noninflammatory lesion counts after 12 weeks of use. Silymarin is known to reduce the production of inflammatory mediators produced by *C. acnes* and also inhibit the migration of neutrophils to the inflammatory site, preventing the release of reactive oxygen species, reactive nitrogen species, and proteolytic enzymes.[22] This may be a possible mechanism of action for its observed benefit in this acne research.

Additionally, in the US/German study, the product was found to be well-tolerated when used as part of a prescription regimen. After 4 weeks of use, more than half the subjects felt that the silymarin antioxidant serum improved skin clarity and desired to continue using the serum after completion of their prescription acne therapy.

The topical silymarin antioxidant serum addresses an emerging acne therapy need with both acne and aging concerns. Thus, a silymarin antioxidant serum can fulfill anti-aging and acne needs on its own or with prescription acne treatment with favorable tolerability. This novel silymarin antioxidant serum was shown to have a significant benefit in reducing acne alone and as part of a cosmeceutical acne regimen or prescription acne treatment. In addition, clinical testing demonstrated significant improvement in skin attributes, providing a possible solution for aging concerns in oily, acne-prone skin.

DISCLOSURES

ZDD and MK received a research grant from L'Oreal to conduct the research presented in this manuscript. HC, SW, and SL are employees of L'Oreal.

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ORIGINAL ARTICLE

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Human Clinical Trials Using Topical Bakuchiol Formulations for the Treatment of Skin Disorders: A Systematic Review

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ABSTRACT

Background: Bakuchiol is a topical cosmeceutical marketed as a retinoid alternative. Human clinical trial data on bakuchiol's efficacy for the treatment of dermatologic conditions has not been thoroughly evaluated.
Objective: To review human clinical trials using topical formulations containing bakuchiol in the treatment of facial skin disorders.
Materials and Methods: A comprehensive electronic search of Cochrane Library, PubMed, EMBASE, and Web of Science was conducted on August 28, 2022, using the search terms "bakuchiol" and "UP256." Study characteristics, measured outcomes, significant results, and stated limitations were extracted.
Results: Fifteen human clinical trials were analyzed. Dermatologic conditions treated included aging, acne, and post-inflammatory hyperpigmentation. Twelve trials were unblinded, open-label trials without a control group. Ten trials used a combination therapy containing bakuchiol. Four trials did not specify the dose or concentration of bakuchiol in treatment regimens. The heterogeneity of treatments, study designs, and measured outcomes makes meta-analysis unfeasible.
Conclusion: Trials lack methodologic rigor, which introduces a high risk of bias in reported outcomes. The use of combination topical formulations containing bakuchiol limits the comparison of bakuchiol's efficacy with retinoids. Continued research with an improved trial design is needed.

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INTRODUCTION

The increasing role of online information in patient decision-making requires that dermatologists be prepared to discuss unsubstantiated dermatologic treatments that patients encounter online.[1-4] An Instagram analysis found that 68% of influencers with over 40,000 followers who post dermatology-related content have no medical credentials, while only 4% were dermatologists.[5] With 93% of skin influencers sharing self-promoted or sponsored content, there is substantial capacity for financial conflicts of interest.[5]

These trends have been accompanied by an increased interest in natural skincare ingredients.[6,7] Bakuchiol is a plant-derived molecule marketed as a natural, mild alternative to retinoids with demonstrated anti-tumor and anti-viral activity. Bakuchiol has been tested in epithelial carcinoma and melanoma cell lines, inhibits melanogenesis in cultured human melanocytes, and has been explored as a treatment for psoriasis.[8-12] Bakuchiol's biologic activity is superficially understood but may be due to the modulation of inflammation and oxidation.[13-19] Methodologic flaws in human clinical trials using bakuchiol for the treatment of facial aging have been reported.[20] A recent review of evidence for bakuchiol's use in dermatology did not capture multiple published human clinical trials.[21]

The objective of this systematic review is an updated analysis comprising all human clinical trial data on the use of bakuchiol in topical formulations for the treatment of facial skin disorders. A broad assessment of evidence for bakuchiol's use as a dermatological treatment will inform its future use in cosmetic dermatology.

MATERIALS AND METHODS

A comprehensive search of Cochrane Library, PubMed/MEDLINE, EMBASE, and Web of Science was conducted on or before August 28, 2022, using the search terms "bakuchiol" and "UP256." Cochrane Library PRISMA guidelines were used for de-duplication, inclusion, and exclusion processes.[22,23] Inclusion criteria were human clinical trials with bakuchiol treatment of skin and English language. Exclusion criteria were basic science articles, epidemiologic studies, case reports, reviews, meta-analyses, skin explant studies, skin cell assay studies,

TABLE 1.

Study Characteristics and Topical Bakuchiol Treatments			
Daily Topical Treatment	**N**	**Study Period**	**First Author**
0.5% bakuchiol 2x	13	12 wks	Brownell[24]
1.5% bakuchiol and 1% *V. tahitensis* 2x	43	8 wks	Bacqueville[25]
0.5% bakuchiol 2x	17	12 wks	Chaudhuri[26]
1% w/w bakuchiol 2x	60	4 wks	Draelos[27]
0.1% melatonin, 0.5% bakuchiol, 10% ascorbyl TIP 1x at night	24	12 or 24 wks	Goldberg[28]
Unk. % bakuchiol 2x	20	4 wks	Lyons[29]
0.5% bakuchiol 2x	44	12 wks	Dhaliwal[30]
30% THD ascorbate 1x daily in morning; 0.5% retinol, unk. % bakuchiol, unk. % *O. japonicus* root 1x at night	44	12 wks	Herndon[31]
Unk. % bakuchiol, unk. % *G. biloba* extract, unk. % mannitol 1x in morning; 0.1% adapalene gel 1x at night	111	8 wks	Polákova[32]
Unk. % bakuchiol, unk. % *G. biloba* extract, unk. % mannitol 2x	38	8 wks	Trompezinski[33]
0.1% melatonin, 0.5% bakuchiol, 10% ascorbyl TIP 1x at night	31-48	12 hrs-4 wks	Goldberg[34]

and non-English language. We extracted details on study characteristics, assessment methods, measured outcomes, treatment formulations, significant results, and stated limitations.

RESULTS

Search results returned 369 non-duplicate articles. Three-hundred fifty articles were excluded after a review of titles and abstracts. Nineteen articles were sought for retrieval, with 8 meeting the criteria for exclusion (review article n=1, ex vivo skin explant study n=1, case report n=1, letter to the editor n=1, and pre-manuscript abstract (duplicate) n=4). The remaining 11 articles met both inclusion criteria for review.[24-34]

These 11 articles represent 15 human clinical trials using topical bakuchiol formulations for the treatment of dermatologic disorders. One article comprised 5 trials conducted by Goldberg et al with the same topical bakuchiol formulation.[34] Twelve trials (80%) were open-label clinical usage trials without a control group. Five trials (33%) treated skin with bakuchiol alone, while the remainder treated skin with a combination of bakuchiol and other active ingredients. Four trials (27%) did not specify the dose or concentration of bakuchiol treatment. The number of participants ranged from 13 to 111, 70% to 100% were female, and the mean age of participants ranged from 18.7 to 58, with 27% of trials not reporting mean age. Table 1 provides key study characteristics and bakuchiol treatment formulations. Table 2 provides an overview of clinical assessments and tools used to measure study outcomes.

Wrinkles

A blinded trial reported a significant decrease in wrinkle depth at week 4 (-7%), week 8 (-13%), and week 12 (-20%).[26] A randomized, double-blind trial observed a decrease in fine wrinkle surface area at week 12 for both bakuchiol (-19%) and retinol (-23%) groups.[30] An open-label clinical usage trial found a decrease in maximum wrinkle relief height at week 4 (-5%), week 8 (-6%), and week 12 (-6%), as well as a decrease in average wrinkle relief height at week 4 (-5%) and week 8 (-5%).[34]

Hyperpigmentation

Goldberg et al observed an increase in the lightness of hyperpigmented skin at week 8 (+2%) and week 12 (+4%), and a decrease in pigmentation in hyperpigmented skin at week 8 (-21%) and week 12 (-35%). The study noticed a decrease in the difference between pigmented and non-pigmented skin at week 12 (-22%).[34] In a separate study, they also reported decreased photodamage and hyperpigmentation assessed by a clinical investigator at week 24.[28]

Retinoid Side Effects

Bakuchiol treatment has increased clinical grading scores of facial dryness at weeks 4 and 8, but not at week 12.[31] However, a randomized blind trial reported that a greater proportion of patients receiving retinol treatment experienced scaling at weeks 4, 8, and 12 compared with bakuchiol treatment.[30] Table 3 provides an overview of reported tolerability and adverse outcomes data from included trials.

Appearance, Texture, and Firmness

An open-label clinical usage trial reported that there was a decreased mean ptosis volume (-0.12 mL) and decreased mean depth (-17%) and volume (-16%) of skin deformation at week 8. In addition, there was an increase in firmness (+35%) and radiance (+20%) at week 8.[25] Bakuchiol was previously shown to significantly decrease skin roughness at week 8 (-10%) and week 12 (-21%).[26] As well, bakuchiol reportedly increased skin firmness (+8%) and decreased skin redness (-70%) at week 12.[34]

TABLE 2.

Clinical Assessments and Instrument Measurements	
Clinician Skin Assessments and Instrument Measurements *(italicized)*	**First Author**
Lesion count at screening, baseline, weeks 4, 8, and 12 Global severity score at screening, baseline, weeks 4, 8, and 12	Brownell[24]
Skin modeling with *FaceScan* at baseline, week 4, and week 8 Skin firmness 11-pt assessment and *Dynaskin* measure at baseline, week 4, and week 8 Skin radiance 11-pt assessment at baseline, week 4, and week 8	Bacqueville[25]
Seven aesthetic parameter 5-pt assessment at baseline, weeks 4, 8, and 12 Skin surface assessment with *Miyomoto Surftest* profilometry at weeks 4, 8, and 12	Chaudhuri[26]
Tolerability 5-pt assessment at baseline and week 4 Efficacy 5-pt assessments at baseline and week 4 *TEWL and triplicate pin probe corneometry* at baseline, first application, and week 4	Draelos[27]
Skin quality 10-pt assessment at baseline and week 12 or 24 Photodamage, hyperpigmentation, and wrinkle 4-pt assessments at baseline and week 12 or 24 Tolerability 4-pt assessment at baseline and week 12 or 24 Global aesthetic improvement assessment at baseline and week 12 or 24 3-mm punch biopsy of treated skin in 5 participants at baseline and week 12	Goldberg[28]
Hyperpigmentation IGA assessment at baseline, weeks 4, 5, 6, and 8	Lyons[29]
Tolerability assessment at weeks 4, 8, and 12 Photography-based assessment of wrinkles and pigmentation at week 12	Dhaliwal[30]
Griffiths' 10-pt efficacy assessment at baseline, weeks 4, 8, and 12 Tolerability assessment at baseline, weeks 4, 8, and 12	Herndon[31]
Lesion count, seborrhea 4-pt, IGA 5-pt acne, and global efficacy 10-pt assessments at baseline, week 4, and week 8 Tolerability 4-pt assessment at weeks 4 and 8	Polákova[32]
Porphyrin count at baseline, weeks 4, 8, and 12 Forehead sebum sample composition analyzed by GC-MS	Trompezinski[33]
Study 1: Skin wrinkle assessment with *Dermatop* Study 1: Skin firmness assessment with *Dynaskin* Study 1: Skin pigment assessment with *Spetrocolorimeter* Study 1: Wrinkles, firmness, redness, and tolerability assessments Studies 2 and 3: *TEWL* measurements at baseline, 30 min and 2, 4, 8, and 12 hours Study 4: Forehead sebum assessment with *Sebumeter SM 815* Study 5: Lesion count at baseline, week 2, and week 4 Study 5: Tolerability assessment at baseline and week 4	Goldberg[34]

GC-MS, Gas Chromatography-Mass Spectroscopy; IGA, Investigator's Global Assessment; TEWL, Transepidermal Water Loss

Skin Composition

An open-label clinical usage trial reported an increase (+16%) in skin moisture content after 4 weeks of treatment.[27] A second open-label clinical usage trial also found an increase in collagen III (+16%) at week 12.[28] In a short-duration trial comparing bakuchiol treatment with untreated skin, bakuchiol treatment increased skin hydration after 4 hours (+44.5%) and 6 hours (+34.4%) and decreased transepidermal water loss (TEWL) at hour 4 (-7.8%) and hour 6 (-8.5%).[34]

Lesion Counts

An open-label clinical usage trial observed a decrease in the mean inflammatory lesion count (-26.9%) at week 8 and (-28.4%) at week 12 compared with baseline.[24] A double-blind clinical trial reported a reduction in the average inflammatory and non-inflammatory lesion counts for both the bakuchiol treatment group (-62.7%) and control group (-41.5%) at the end of the study.[32] Bakuchiol treatment also reduced the number of comedones in 82% of subjects at week 2 and 85% of subjects at week 4.[34]

Porphyrins

In an open-label clinical usage trial, bakuchiol has previously been shown to decrease the average porphyrin parameter on the frontal face at days 28 and 56 and decrease the average porphyrin parameter on the right and left sides of the face at days 28, 56, and 84.[33]

Sebum

Bakuchiol treatment altered sebum content, resulting in increased non-oxidized squalene at week 8 (+27%) compared with day 0; decreased (-10%) oleic acid at week 8 compared with

TABLE 3.

Reported Tolerability Adverse Events and Discontinued Participants		
Discontinued Due to Tolerability Issues	**Reported Adverse Events from Bakuchiol Topical Treatment**	**First Author**
None	Investigator: Erythema, dryness, scale, oiliness, postinflammatory hyperpigmentation Participants: Pruritis, burning, skin discomfort	Brownell[24]
Unreported	Unreported	Bacqueville[25]
Unreported	Unreported	Chaudhuri[26]
None	Investigator: none Participants: 10% (6/60) minimal stinging with application, 5% (3/60) minimal tightness	Draelos[27]
None	Investigator: 4% (1/25) mild dryness and scaling Participants: 8% (2/25) mild tingling, 8% (2/25) mild itching	Goldberg[28]
Unreported	Unreported	Lyons[29]
None	Investigator: Skin redness greater in bakuchiol group but scaling greater in retinol group Participants: Itching	Dhaliwal[30]
None	Investigator: 3 temporary discontinuations due to mild effects Participants: 23 subjects had at least 1 local adverse event of burning, erythema, desquamation, or pruritis	Herndon[31]
3 temporary discontinuations	Investigator: 3 temporary discontinuations due to mild effects Participants: 23 subjects had at least 1 local adverse event of burning, erythema, desquamation, or pruritis	Polákova[32]
Unreported	Unreported	Trompezinski[33]
None	Study 1: Two participants reported mild red papules and moderate erythema, dryness, and desquamation of skin. Authors report adverse events not attributable to topical treatment. Study 2-5: None reported by either investigator or participants	Goldberg[34]

GC-MS, Gas Chromatography-Mass Spectroscopy; IGA, Investigator's Global Assessment; TEWL, Transepidermal Water Loss

day 0; increased linoleic acid at week 4 (+29%) and week 8 (+37%) compared with day 0; and increased sapienic acid at week 8 (+10%) compared with day 0.[33] Bakuchiol has also reduced mean forehead sebum secretion after 4 weeks (-18.2%).[34]

Post-Inflammatory Hyperpigmentation (PIH)

In an open-label clinical usage trial, 8 subjects with PIH scores >2 at baseline had a decrease in facial PIH involvement at week 8.[24] A nonrandom clinical trial also reported that bakuchiol significantly decreased the pigmentation of acne lesions.[29]

DISCUSSION

We identified 15 human clinical trials using topical formulations containing bakuchiol for the treatment of aging, acne, hyperpigmentation, transepidermal water loss, eczema, rosacea, cosmetic intolerance syndrome, and oily skin. The majority of trials (67%) did not treat skin with bakuchiol alone, instead using formulations containing additional ingredients such as plant extracts (*Vanilla tahitensis, Ginkgo biloba, Ophiopogon japonicus* root), Vitamin C (ascorbate, ascorbyl tetraisopalmitate, tetrahexyldecyl ascorbate), mannitol, and melatonin. Measurements of topical treatment efficacy included clinical assessment scales, skin biopsy, facial scanning or photography, and participant self-reported data.

Evaluating the efficacy of topical bakuchiol formulations from trial data is difficult, as 80% of trials are non-randomized, non-blinded, open-label clinical trials lacking a vehicle control group. For the 3 trials using controls, 2 used topical vehicle controls while one used a retinol control group. Trial outcomes measured by clinical grading and participant-reported data hold a significant risk of bias as both participants and trial personnel may have been aware of receiving experimental treatment. In 2020, Spierings emphasized that reported methodologic designs did not align with the trials as executed, and that results were incongruent with the reported study design.[2] Specifically, Chaudhuri and Bojanowski reported that their study design was blinded but that the trial did not include a control group.[2,6] Dhaliwal et al reported that their study was double-blind, yet the experimental group administered topical bakuchiol treatment twice daily while the control group administered retinol treatment once daily, suggesting an inability to blind the study due to different treatment regimens.[2,7]

With 67% of trials using combination treatments containing more than bakuchiol and 27% failing to report the dose or concentration of bakuchiol in experimental treatment formulations, it is also difficult to delineate how much of the observed clinical trial results were due to bakuchiol's activity alone. Of the 5 studies

using an experimental treatment containing only bakuchiol, 3 used 0.5% bakuchiol topical treatment administered twice daily.

Consistent limitations of study designs included 20% of trials reporting a small sample size as a limitation, 53% of trials reporting a short study period as a limitation, and 53% of trials reporting the lack of vehicle control groups as a limitation. Additionally, 53% of trials used participants' self-reported data but did not necessarily discuss this as a limitation of trial results. The heterogeneity of bakuchiol treatment formulations and measured outcomes makes meta-analyses of trial results unfeasible.

Despite these limitations, trials provided a wealth of measurement modalities. Though clinical grading and self-reported data have a high risk of bias in the context of included trial designs, other trial measures may be more reliable and provide greater confidence in reported trial results. These include various digital skin scanning and imaging tools, computer algorithms, and validated clinical assessments (see Table 2).

Clarifying the efficacy of topical bakuchiol formulations for the treatment of skin disorders will require an improved human clinical trial design. Future studies should consider the adoption of a double-blind, randomized vehicle-controlled trial with a clearly defined bakuchiol monotherapy, large sample size, and longer study duration. Although changes in gene expression in cells treated with bakuchiol have been described, future studies should revisit bakuchiol's pharmacology to further elucidate its mechanisms of action in the skin.[6]

CONCLUSION

This review presents human clinical trials of topical bakuchiol formulations for the treatment of skin disorders. While studies report improvements in facial skin after treatment with topical formulations containing bakuchiol, the trials lack methodologic rigor, creating a high risk of bias in reported outcomes. No trials used a randomized, double-blind, vehicle control design with specified bakuchiol treatment. Current evidence of bakuchiol's efficacy as a retinoid-like molecule is limited by its use in combination topical formulations. Existing studies do not provide sufficient data to evaluate its retinoid-like effects and do not support the continued adoption of bakuchiol in cosmetic formulations based on claims of efficacy comparable with retinoids. Future studies should use bakuchiol treatment without other topical agents. To truly elucidate bakuchiol's efficacy for the treatment of dermatologic disorders, continued research with improved study design is needed.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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COVID-19 Protection Strategies: Lessons Learned About Epidermal Barrier Function and the Significance of Optimized Skin Care

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ABSTRACT

Initially categorized as primarily a respiratory disease, COVID-19 can involve other organ systems and may have direct skin manifestations, including exanthems, morbilliform eruption, generalized urticaria, or pseudo-chilblains —commonly called "COVID Toes." Frequent handwashing and prolonged wearing of face masks and shields in efforts to minimize transmission of SARS-CoV-2, the novel coronavirus that causes COVID, has given rise to indirect skin manifestations of COVID. "Maskne" and handwashing dermatitis are particularly common among healthcare workers.

Characterized by skin inflammation, dryness, pruritus, and other symptoms, these conditions are fundamentally disorders of skin barrier dysfunction. This dysfunction may result from the combination of mechanical skin damage, changes in skin pH, reductions in skin lipids attributable to protection measures, and local alterations in the cutaneous microbiome. Strategies to manage these conditions focus on reversing and repairing skin barrier damage with preventative general measures, optimized skin care with the selection of proper products, eliminating irritant exposures, and avoiding certain medications, such as topical corticosteroids, that may further impair barrier function despite temporary improvement in signs and symptoms.

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INTRODUCTION

The COVID-19 pandemic represented an unprecedented global health emergency. Initially categorized as primarily a respiratory disease, the disease can involve other organ systems and may have direct skin manifestations, including exanthems, morbilliform eruption, generalized urticaria, or pseudo-chilblains—commonly called "COVID Toes".[1-3]

Millions of people around the world wore face masks and shields for prolonged periods in efforts to minimize transmission of SARS-CoV-2, the novel coronavirus that causes COVID. Additional risk mitigation strategies included frequent handwashing and glove-wearing. Although the height of the pandemic has long passed, many individuals, organizations, and healthcare facilities still continue the practice of wearing face masks.

These safety strategies have given rise to indirect skin manifestations of COVID, particularly among healthcare workers.[4] In fact, the effects on the facial skin from long-term mask-wearing has been popularly termed "maskne." "Maskne" and handwashing dermatitis are particularly common among healthcare workers.[5]

The skin signs of maskne can be consequential for affected individuals. It is interesting to note that another risk mitigation strategy common in the era of COVID-19, frequent handwashing, is also associated with a skin manifestation in the form of hand dermatitis, characterized by excessive dryness, scaling, erythema, and even skin tears and fissures. Handwashing is important in healthcare facilities to prevent infection, and such preventative measures are important to carry out consistently.[6]

However, excessive washing of hands, often a compulsive behavior by some individuals in their everyday life beyond what is reasonable and practical, is fraught with adverse effects on skin primarily related to significant skin barrier damage and the potential for adverse effects on the skin microbiome. Once the skin is affected with marked xerosis and dermatitis, handwashing and mask-wearing may become painful, leading to the potential for individuals to become lax regarding safety measures and thus putting themselves and others at risk for exposure to infection.

The detrimental skin manifestations of prolonged mask-wearing and frequent handwashing share a common cause: disruption of the skin barrier and deterioration of its function. Therefore, strategies aimed at barrier repair and protection may be beneficial in reversing and preventing these negative skin changes and concerns.

MATERIALS AND METHODS

The Epidermal Barrier in Review

The epidermal skin barrier is commonly conceptualized as a "bricks and mortar" construct. Mature, hydrophobic corneocytes — characterized by keratin filaments embedded in a fillagrin-rich barrier protein matrix — stack together in layers that are held in place by corneodesmosomes and an extracellular lipid matrix. However, unlike a brick wall, this "mortar" is dynamic as it adapts to changes in skin exposures, serving to provide epidermal cohesion, maintain a functional permeability barrier, and sustain optimal epidermal water content.[7,8]

The lipid matrix is composed of cholesterol, ceramides, and free fatty acids.[9] Ceramides constitute the greatest proportion of the lipid matrix in healthy skin, at 40% to 50%, while the remainder consists of approximately 25% cholesterol and 10% to 20% free fatty acids. The unique structure of the stratum corneum allows for epidermal penetration via the transcellular route, directly through the corneocytes, the intercellular route, navigating through the lipid matrix or the pilosebaceous route by gaining access through the follicular orifice.[10] The lipid matrix serves to permit the flow of water and electrolytes out of the skin or to facilitate the absorption of substances, such as medications, allergens, and microbes through the skin.[11]

It has been demonstrated that the physiological properties of these lipids, in this specific composition, enable the stratum corneum to perform its primary function of maintaining homeostasis by regulating water content, regulating water flux, and modifying transepidermal water loss (TEWL) as needed to maintain homeostasis within the skin.[12,13]

The protective role of the skin barrier in keeping foreign bodies out is perhaps more readily appreciated than its sophisticated function of modulating epidermal hydration and a relatively stable microbiome. Natural moisturizing factor (NMF) works in harmony with the intercellular lipid layer, epidermal barrier proteins, and other epidermal constituents to help maintain the water balance in the epidermis.[14] NMF is composed of free amino acids, pyrrolidone carboxylic acid (PCA), urocanic acid, lactic acid, and urea, all of which are humectants.[15] It is produced by filaggrin.[14]

When epidermal barrier integrity is damaged, excess moisture passes out of the skin, resulting clinically in xerosis (dry skin). TEWL is recognized as an objective measurement to assess the barrier function of skin.[16] As barrier function decreases, TEWL increases.

Sebum produced by the sebaceous glands also plays a modest role in skin moisturization. Sebum is a waxy substance that serves to lubricate the skin and reduce adverse frictional changes, among other functions.[17]

An important feature of a healthy epidermal barrier is an acidic pH, once dubbed the "acid mantle."[18] The importance of skin pH has long been recognized, as has the fact that topical skin care can influence skin pH. Yet, when it comes to skin care and even topical prescription vehicles, sometimes dermatologists have overlooked the impact of pH when prescribing treatments or recommending moisturizers and cleansers.[29]

Skin pH naturally is acidic, in the range of 4.0 to 6.0, and normal pH is associated with a decreased incidence of skin diseases and infection.[20] Tap water is neutral, in the range of 7.0 to 8.5. True bar soaps are alkaline, in the range of 10.0 to 12.0. Modulation of the barrier pH leads to changes in barrier function. Glucosylcerebrosidase is an enzyme that helps form ceramide from glucosylceramide. Its activity has been shown to be reduced by 10-fold at pH 7.4, compared to pH 5.5.[19]

Notably, a physiological skin pH acts as an antimicrobial defensive mechanism. The skin's naturally acidic pH is shown to inhibit pathogenic organisms Staphylococcus aureus and *Streptococcus pyogenes*. At normal skin pH, the regulation of antimicrobial peptides produced from keratinocytes, neutrophils, and mast cells is optimized.[21] Changes in pH are reported to play a role in the pathogenesis of skin diseases such as irritant contact dermatitis, atopic dermatitis, ichthyosis, acne vulgaris, and Candida albicans infections.[22] Conversely, normalizing the pH by acidification through topical product application has been shown to help establish a physiological microbiota, reduce skin barrier dysfunction, promote physiologic epidermal differentiation, and reduce inflammation.[23]

Endogenous factors, such as skin moisture, sweat, sebum, and age, can influence the skin pH, as can exogenous factors, such as detergents, cosmetic and skincare products, medications, and occlusion.

COVID Mitigation Strategies and Barrier Dysfunction

COVID-19 mitigation and self-protection measures, while necessary and largely effective, can be detrimental to optimal epidermal barrier function, leading to clinical signs of dermatitis. "Maskne" is, of course, a misnomer. The condition in question is not related to acne vulgaris and it is not known to be mediated by C. acnes or any of the other key pathogenic factors that drive acne. It is, however, an illustrative case of a skin barrier disorder. The combination of an underlying warm and moist environment

created by occlusion and the mechanical and frictional damage from the mask or its bands, coupled with changes in skin pH and disruption of the chemical composition of the barrier, gives rise to physical manifestations of erythema, scale, pruritus, and discomfort.

Face masks can create friction on the cheeks, mechanically damaging the skin barrier and potentially causing maceration. Additionally, masks can trap moisture from respiration and perspiration, which can alter the pH of the skin and accelerate barrier disruption.

Frequent handwashing is detrimental to proper barrier function. A single cleansing can strip sebum and reduce surface lipids, initiating an immediate drying of the skin.[6] Many soaps are alkaline, altering the skin's pH with consistent use.[6]

Repeated washing with alkaline soaps can, according to researchers at the US Centers for Disease Control, "be associated with long-standing changes in skin pH, leading to a reduction in fatty acids, and subsequent changes in resident flora."[24]

Dysbiosis of the microbiome can lead to the overpopulation of pathogenic microbes and their inflammatory byproducts, inciting a cycle of continued skin damage.[25] It is possible that pathogenic microbes could proliferate to the point of causing secondary bacterial or fungal infections at affected skin sites and can be transferred to other individuals.

In efforts to counteract xerosis, scaling, pruritus, and other visible signs of skin barrier disruption on the face and hands, patients may apply lotions and moisturizers, some of which can paradoxically cause further degradation of skin barrier function. Moisturizers and other skincare products that are not optimized for barrier support can negatively impact skin pH and other physiologic barrier properties.[26] Others may even contain irritants and/or allergens that can further cause visible contact dermatitis or subclinical damage to the epidermal barrier that reduces epidermal integrity.[27]

Inflammation is a pathophysiologic consequence of both maskne and dermatitis secondary to handwashing, which may lead some affected individuals or their physicians to consider the use of topical corticosteroids for management. Although potentially beneficial in the short term to clear the visible eruption and itching, this therapeutic strategy is likely to be detrimental if not coupled with proper skin care and moisturization and with appropriate recommendations for their use. Even short-term use of topical corticosteroids has been shown to reduce epidermal barrier function, marked by decreased synthesis of lipids and lipid lamellae.[25,28] Topical application of corticosteroids has been shown to result in an increase in TEWL after discontinuation of use for acute inflammation due to the reduction in the epidermal lipids needed to maintain physiologic stratum corneum water content.[29]

Effective Management of Barrier Disruption

Despite concerns with some topical moisturizers, it must be noted that well-formulated moisturizers represent the most appropriate adjunctive tool for reducing and improving the symptoms of barrier dysfunction caused by a variety of exogenous sources, including changes in humidity, use of true soaps that are alkaline, over-washing, excessive bathing, excessive exfoliation, and exposures to irritants and allergens. The key is appropriate skincare product selection and topical therapy optimized to support barrier function.

One specific product has a history of invested scientific rigor regarding its formulation, effective use for skin barrier dysfunction, and positive therapeutic outcomes in patients with atopic dermatitis and provides an illustrative example of the importance of formulation selection. A ceramide-dominant, physiologic lipid-based barrier repair emulsion, EpiCeram® Skin Barrier Emulsion (PuraCap Pharmaceutical, Iselin, NJ) is a 510K prescription medical device product that is United States Food and Drug Administration (FDA)-cleared and indicated for the treatment of dry skin conditions and to manage and relieve the burning and itching associated with various types of dermatological conditions including atopic dermatitis, irritant contact dermatitis, and radiation dermatitis. It is corticosteroid-free and fragrance-free.

EpiCeram has a 3:1:1 molar ratio of ceramides, cholesterol, and free fatty acids. This ratio has been identified as an optimal ratio to help skin barrier repair and has shown to simulate the relative amount of these same three lipid components in the endogenous intercellular lipid membrane of the stratum corneum.[30] Importantly, the topical formulation has a pH of 5, helping to maintain the physiologic acidic pH of the stratum corneum.

The original formulation contains ceramide (pseudo-ceramide-104 or PC-104), conjugated linoleic acid (CLA), and cholesterol in an emollient base, delivered via a patented time-released system (MultiSal Neolipids). While natural ceramides may be associated with inhibition of keratinocyte growth, the non-toxic pseudo-ceramide (PC-104) is not associated with detrimental effects on keratinocytes.[30]

The EpiCeram formulation is designed to facilitate the slow release of PC-104, CLA, and cholesterol, allowing for a once-daily application that provides 24-hour barrier repair benefits. MultiSal™ Neolipids is a multi-compartment microencapsulation system that allows the release of different functional ingredients at the same location but at different times. When the emulsion is rubbed onto the skin, the initial outer 30-micron nanosphere

shell dissolves. This releases sub-micron spheres infused with the physiologic lipids (CLA) that release their contents slowly over time. Additionally, encapsulation appears to stabilize the free fatty acid.[31]

In the pivotal trial of the ceramide-dominant, physiologic lipid-based barrier repair emulsion, efficacy was compared to fluticasone propionate cream 0.05% in pediatric patients with moderate-to-severe atopic dermatitis.[32] The trial involved 121 patients with moderate-to-severe atopic dermatitis. At days 14 and 28, the ceramide-dominant, physiologic lipid-based emulsion reduced clinical disease severity, decreased pruritus, and improved sleep habits. Although fluticasone cream provided a significantly greater improvement on the SCORing Atopic Dermatitis (SCORAD) tool, as well as in pruritus and sleep habits at day 14, by day 28 the agents showed comparable efficacy for all measures.

In an open-label, interventional study assessing efficacy and satisfaction with the ceramide-dominant, physiologic lipid barrier repair emulsion in patients with atopic dermatitis, about half of the participants achieved success as measured by investigator global assessment (clear or almost clear scores) at 3 weeks. Three-quarters of the participants and 77% of investigators reported satisfaction with therapy after 3 weeks of treatment.[30]

CONCLUSION

The COVID-19 pandemic led to the widespread, long-term wearing of face masks and gloves as well as frequent handwashing, especially in healthcare settings. Although these were extremely important measures to follow, they did elicit negative effects on the skin barrier, leading to epidermal barrier dysfunction, inflammation, and even skin maceration, tears, and fissures. An important sequela of this pandemic has been a heightened recognition and awareness of the importance of maintaining proper daily skin care. The thoughtful selection and use of optimally formulated skin cleansing and moisturizing products can help to prevent and repair epidermal barrier damage. Importantly, selected products should be compatible with the physiological pH of the skin, replace or support key components of the stratum corneum, especially the intercellular lipid matrix, and sustain the moisture content of the skin without the presence of potential allergens or irritants. A product that optimizes patient convenience with once-daily application may be preferred. The use of topical corticosteroids to manage skin inflammation of "maskne" or handwashing dermatitis is often not optimal, as these products may further damage the epidermal barrier and can induce facial eruptions, such as perioral dermatitis. Of note, the ceramide-dominant, physiologic lipid-based barrier repair emulsion has been shown to have efficacy comparable to topical fluticasone in appropriately selected cases of eczematous dermatitis. When the severity of inflammation warrants use of a topical corticosteroid in the judgment of the clinician, adjunctive use of the ceramide-dominant, physiologic lipid-based barrier repair emulsion is a recommended approach to combat the barrier impairment (reduced epidermal lipid synthesis) associated with topical corticosteroid use.

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ORIGINAL ARTICLE

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Comparing the Safety and Effectiveness of Microfocused Ultrasound: Standard Versus Targeted Tissue Protocol in Lifting and Tightening the Lower Face and Upper Neck

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ABSTRACT

Background: Micro-focused ultrasound with visualization (MFU-V) delivers energy to specific soft tissue layers beneath the epidermis with the ability to lift and tighten the lower face and neck.
Objective: To determine the efficacy of microfocused ultrasound with visualization (MFU-V) using a standard treatment line protocol versus a customized treatment line protocol based on the patient's unique anatomy targeting the superficial muscular aponeurotic system and fibrous septae for lifting and tightening of the lower face and neck
Methods: This was a single center, prospective, randomized, investigator blinded clinical trial. 51 subjects were randomized to receive a single treatment of MFU-V targeting the lower face and neck using either a standard or custom treatment protocol.
Results: Subjects in both standard and custom treatment groups noted a greater than one point improvement in jawline laxity. Three-dimensional photography measurements also demonstrated lifting of the lower face and neck in both treatment groups.
Conclusion: Custom and standard treatment MFU-V protocols produce a safe and effective treatment for tightening and lifting the lower face and neck. Custom treatment protocols aid in maximizing results for patients with variations in the anatomy of the lower face and neck.

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INTRODUCTION

A well contoured jawline is a key factor in the perception of facial attractiveness and youthfulness in both men and women.[1-3] Patients are increasingly interested in non-invasive methods with little to no downtime to improve jowling and sagging of the lower face and neck. These changes are caused by loss of bone, subcutaneous fat repositioning, loosening of facial ligaments, and a decrease in collagen and elastin fibers within the dermis and subcutis.[4] Microfocused ultrasound with visualization system (MFU-V) (Ulthera Inc., Ultherapy®, Merz North America, Inc., Raleigh, NC) delivers ultrasound energy below the epidermis creating precise 1 mm^3 microthermal lesions at approximately 65°C in specific anatomical layers of the skin including the dermis at 1.5 mm of depth, deep dermis at 3.0 mm of depth and the sub-dermal plane including the superficial musculo-aponeurotic system (SMAS) and fibrous septae at 4.5 mm.[5,6] MFU-V has the ability to bypass the epidermis, therefore; eliminating the downtime created by many non-ablative and ablative devices used for neocollagensis.[7] MFU-V is based on principles of wound healing to produce robust neocollagenesis which creates lifting and tightening of the treated tissue.

Treating all patients with a one size fits all standard protocol does not take into consideration variances in facial anatomy and skin tissue thickness and may result in suboptimal results and poor patient satisfaction.[8] Customizing the dual depth treatment protocol to the anatomy of each patient by visualizing the superficial muscular aponeurotic system (SMAS) and fibrous septae of the lower face and upper neck, which in some subjects can be found at 4.5 mm deep and in others at 3.0 mm deep, and then selecting the appropriate depth transducers

may result in a more efficacious treatment with higher patient satisfaction as all coagulation point placement is being optimized.[9]

MATERIALS AND METHODS

This was a single center, prospective, randomized, investigator blinded clinical trial. Institutional review board approval was obtained to ensure the study was conducted in accordance with the Declaration of Helinski and the International Conference on Harmonization. After obtaining informed consent, 51 female subjects were enrolled in the trial, with a median age of 55, and Fitzpatrick skin types II-V. Subjects had moderate to severe sagging of the jawline area (grade II-III on the Merz Jawline Assessment Scale). Subjects were excluded if they were pregnant, breastfeeding, or planning pregnancy for the duration of the trial. Additionally, subjects were excluded if they were using any opioids for pain control. Exclusions also included the presence of active or local systemic skin disease that may affect wound healing, history of Bell's palsy, significant scarring in the area, open wounds, severe or cystic acne in the treatment area, active implants (pacemakers or defibrillators) or metallic implants in the area (dental implants not included). History of microdermabrasion or glycolic acid peel to the treatment area within two weeks prior to study participation. History of any energy based device procedure for skin tightening within the past 12 months, injectable filler of any type in the treatment area within the past 24 months, neurotoxin treatment in the area within the past six months, fractional and fully ablative resurfacing laser treatment within the past 6 months, surgical dermabrasion or deep facial peels within the past 6 months, history of facelifts, neck surgery within the past two years, any history of deoxycholic acid or cryotherapy to the treatment area, history of contour threads in the past year or initiation of retinoids 14 days prior to the start of the study, use of antiplatelet/anticoaugulants, systemic immunosuppressants, and/or autoimmune connective tissue disease.

Subjects were randomized to receive 1 MFU-V treatment of the lower face and upper neck utilizing either the standard or custom dual depth treatment protocol. The standard treatment protocol included 360 lines with the 4.5 mm transducer followed by 310 lines with the 3.0 mm transducer, both at the default energy level setting of 2. The custom dual depth treatment protocol was based on the patient's unique anatomical depth of the SMAS of the lower face and the platysma of the upper neck using visualization on the device. 360 lines were delivered with either the 4.5 mm or the 3.0 mm transducer, depending on the depth of the SMAS and platysma followed by 310 lines with the 3.0 mm depth transducer, or the 1.5 mm transducer depending on the depth of the fibrous septae. Prior to treatment, subjects were offered oral pre-medication of 5-10 mg of diazepam, 800 mg of ibuprofen, and/or 1 gram of acetaminophen. Immediately post treatment, subjects were asked to rate their level of discomfort during treatment using a 10-point visual pain scale (0= no pain, 10= worst pain). Subjects returned for follow up visits at month 3 and month 6 for evaluations. Vectra 3D photographs (Canfield Scientific Inc., Parsippany, New Jersey) were taken at baseline, month 3, and month 6. 3D photographs were then analyzed with Mirror Photofile Software (Canfield Scientific Inc., Parsippany, NJ) to measure submental lift. The following evaluations were also conducted: Blinded Evaluator Merz Jawline scale (0= no sagging, 1= mild sagging, 2= moderate sagging, 3= severe sagging, 4= very severe sagging; Figure 1) at day 0, month 3 and month 6; and Investigator Global Aesthetic Improvement Scale (I-GAIS) (1= Very Much Improved, 2= Much Improved, 3= Improved, 4= No change, 5= Worse), Subject Global Aesthetic Improvement Scale (S-GAIS) (1= Very Much Improved, 2= Much Improved, 3= Improved, 4= No change, 5= Worse) and Subject Satisfaction Questionnaire (0= Completely Dissatisfied, 1= Moderately Dissatisfied, 3= Neither Dissatisfied Nor Satisfied, 4= Mildly Satisfied, 5= Moderately Satisfied, 6= Completely Satisfied), were conducted at month 3 and month 6. Any adverse events were recorded.

Statistical Analyses

All statistical tests were two-sided and interpreted at a 5% significance level. Descriptive statistics (ie, mean standard deviation, etc) were provided for all continuous variables and frequencies for all categorical variables. In order to track changes for individual variables across all relevant visits, single-

FIGURE 1. Merz Jawline Scale (0=no sagging, 1=mild sagging, 2=moderate sagging, 3=severe sagging, 4=very severe sagging).

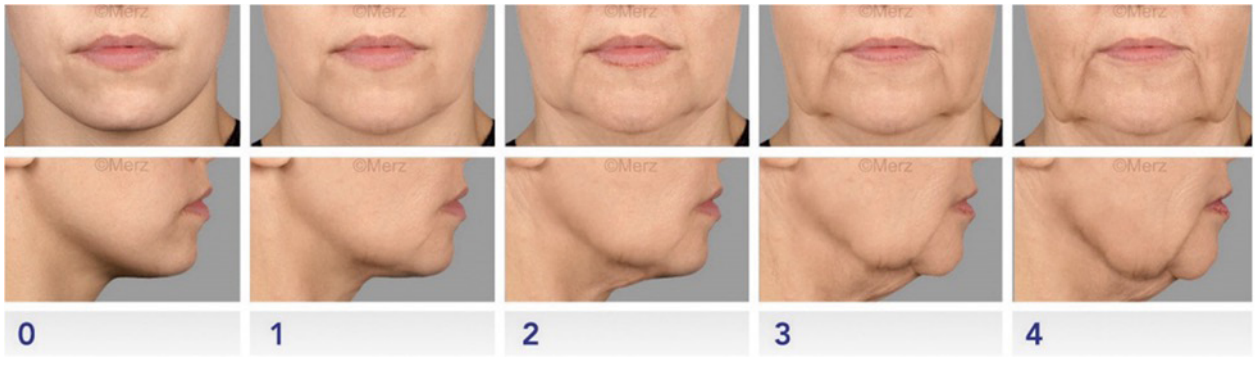
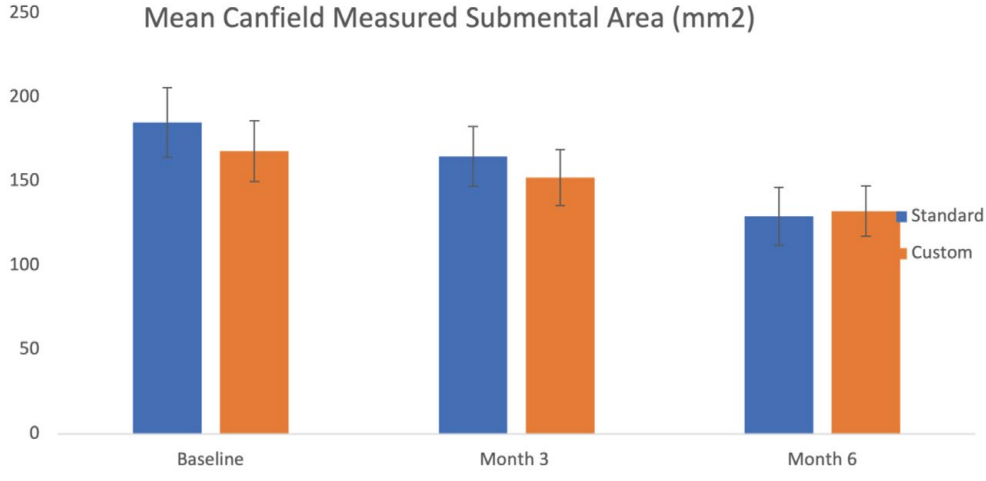


TABLE 1.

Both Standard and Custom Groups Demonstrated Improvement in Submental Lift as Measured by 3D Photography



factor Analysis of Variance (ANOVA) tests were used, while comparisons between two individual visits were done using two sample t-tests assuming equal variance. *P*-values < 0.05 were considered clinically significant.

RESULTS

Forty-one subjects completed the trial, Fitzpatrick II-V skin types, with a mean age of 55 (37 to 65 years old). Nineteen subjects were randomized to the standard treatment group and 22 subjects were randomized to the custom treatment group. Of the subjects randomized to the custom treatment group, 13 subjects still had platysma identified at 4.5 mm and were treated with the 4.5 mm and 3.0 mm depth transducers. 9 subjects had a more superficial platysma at 3.0 mm and were treated with the 3.0 mm and 1.5 mm depth transducers. Seven subjects were lost to follow up and three subjects withdrew consent, as this study took place during the COVID-19 pandemic.

Primary Endpoint

Standard and custom treatment groups both demonstrated improvement with regards to the degree of submental lift as measured by 3D photography (Table 1, Figures 2-4). No statistical significance was noted between groups with regards to submental lift. The mean submental area for the standard group was 185.083 mm^2 ± 101.44 at baseline decreasing to 164.78 mm^2 ± 85.11 at month 3 with further reduction at month 6, 129.11 mm^2 ± 75.06. For the custom group, the mean submental area at baseline was less at 167.85 mm^2 ± 87.20. Reduction in mean submental area was also seen in the custom group with month 3 mean submental area of 152.6 mm^2 ± 80.34 and month 6 being 132.28 mm^2 ± 68.56,

The mean submental lift was 23.28 mm^2 ± 74. 31 at month 3 and 55.52 mm^2 ± 80.60 at month 6 for the standard treatment group.

FIGURE 2. Forty-nine-year-old woman treated with 4.5 mm and 3.0 mm transducers demonstrating a 63% reduction in submental area from baseline to day 180.

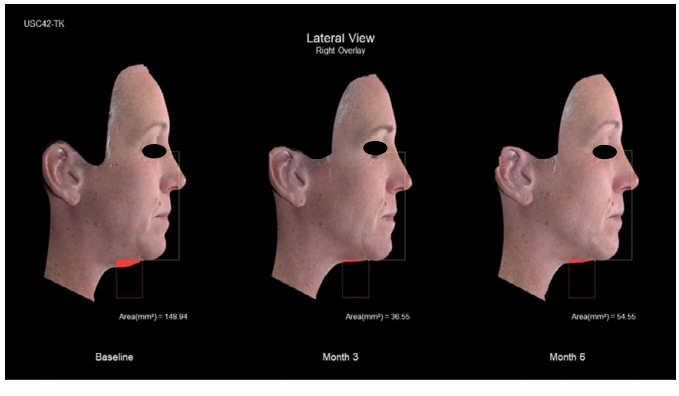


FIGURE 3. Fifty-nine-year-old woman treated with 4.5 mm and 3.0 mm transducers demonstrating a 57% reduction in submental area from baseline to day 180.

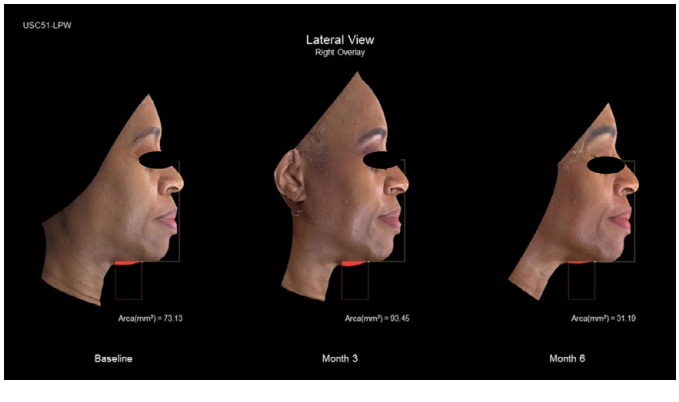


FIGURE 4. Fifty-two-year-old woman treated with 3.0 mm and 1.5 mm transducers demonstrating a 38% reduction in submental area from baseline to day 180.

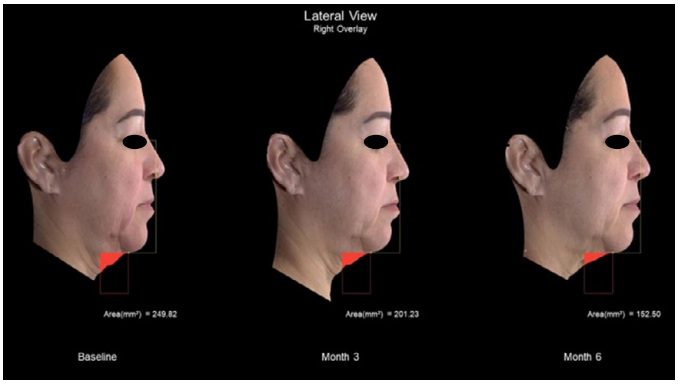
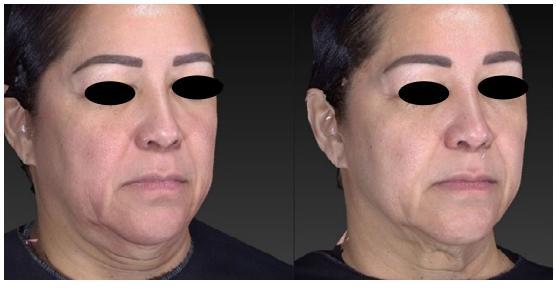


FIGURE 5. Forty-nine-year-old woman 6 months post one standard MFU-V treatment to the lower face and upper neck 4.5 mm and 3.0 mm transducers.

FIGURE 6. Fifty-nine-year-old woman 6 months post one custom MFU-V treatment to the lower face and neck utilizing the 4.5 mm and 3.0 mm transducers.

FIGURE 7. Fifty-two-year-old woman 6 months post one custom MFU-V treatment to the lower face and neck utilizing the 3.0 mm and 1.5 mm transducers.



The mean submental lift was 15.69 mm^2 ± 49.60 at month 3 and 36.15 mm^2 ± 58.10 at month 6 for the custom treatment group.

The mean percent change in submental lift from baseline to month 3 was 11.33% and 9.20%, in standard and custom groups respectively (Table 2). The mean percent submental lift from baseline to month 6 was 28.86% and 20.80% for standard and custom treatment groups, respectively.

Secondary Endpoints

Both standard and custom group treated subjects showed a statistically significant improvement in jawline laxity according to the Blinded Evaluator Merz Jawline Scale from screening to month 6 (P<0.01, Single Factor ANOVA; Table 3, Figures 5-7). The Merz jawline scale at baseline to month 6 for the standard group was 2.38 ± 0.58 and 1.42 ± 0.77, respectively. The Merz jawline scale for baseline to month 6 for the custom group was 2.56 ± 0.50 and 1.45 ± 0.86, respectively. The standard group showed a 0.95 change on the Merz Jawline 5-point scale at month 6, and the custom group showed a 1.11 change on the Merz Jawline 5-point scale at month 6. Seventy-four percent of subjects in the standard group and 77% of subjects in the custom group had a ±1-point improvement in jawline laxity at month 6 according to the Merz Jawline Scale.

At month 6, the custom group showed a statistically significant improved mean I-GAIS than those in the standard group, (P=0.01, two-sample t-test; Figure 5). At month 6, the standard group mean I-GAIS was 2.68 ± 1.20 ("improved") and the custom group mean I-GAIS was 1.77 ±1.02 ("much improved").

There was no statistically significant difference between S-GAIS in standard and custom treatment groups. Overall, the majority of subjects in both groups noted their GAIS was "much improved". The mean S-GAIS at month 6 for the standard group was 2.16 ± 0.96 and the custom group was 1.82 ± 0.96.

At month 3 and month 6, subject satisfaction scores for both groups were positive. At month 3, subject satisfaction scores were 4.56 ± 1.47 and 4.75 ± 1. for standard and custom groups, respectively, with both groups moderately satisfied with their results. At month 6, subject satisfaction scores were 5.05 ± 1.08 and 5.04 ± 1.50, respectively, with both groups moderately satisfied with their results.

Both standard and custom groups rated the pain during treatment similarly, with the standard group rating a 6.16 ± 1.25 and the custom group rating a 6.24 ± 1.53. There were no adverse events.

DISCUSSION

It is well known that a combination of 4.5 mm and 3.0 mm transducers causes a significant lift of the skin underneath the submentum.10-13 Oni and colleagues saw an average submental lift of 45.^{2} mm^2 delivering 295 lines in the lower

TABLE 2.

Percent Change in Submental Measurement From Baseline to Month 3 and Baseline to Month 6 in Standard and Custom Treatment Groups. A negative percent change indicates increased submental lift.

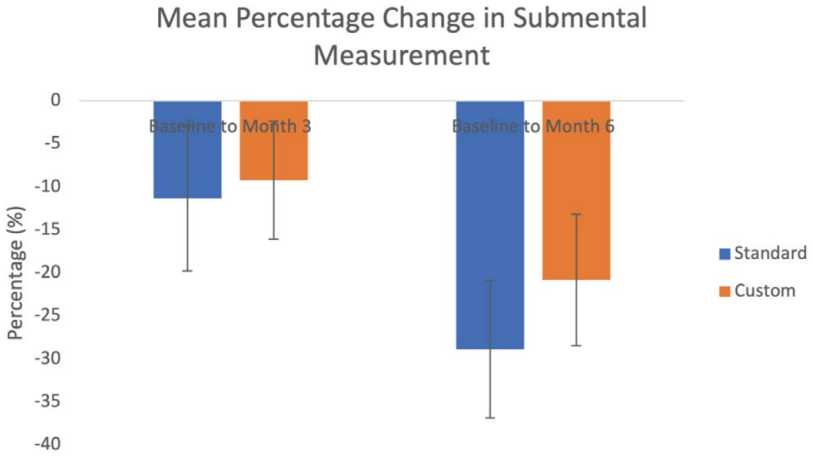
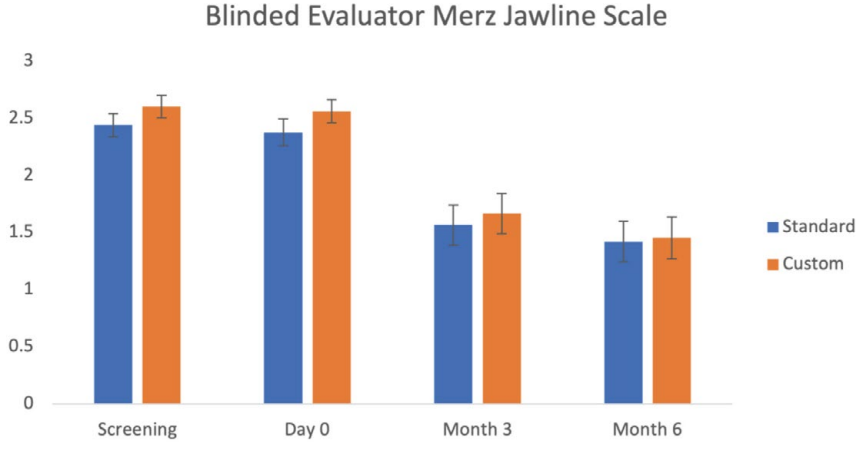


TABLE 3.

A Statistically Significant 1 Point Improvement in Jawline Laxity was Noted in Both Groups From Screening To Month 6, (*P*<0.01, Single Factor ANOVA)



face and neck with the 4.5 and 3.0 mm depth transducers.[13] Our results demonstrate that when the SMAS and platysma are found and targeted at a more superficial depth of 3.0 mm, and then followed by treatment with a 1.5 depth transducer, we can produce a submental lift that is noninferior to patients receiving the standard treatment protocol using the 4.5 mm and 3.0 mm depth transducers. In this study, we found that of the 22 subjects randomized to the custom arm, 41 % of the time (n = 9), their platysma and SMAS were found to be more superficial at 3.0 mm.

In order to provide a more thorough evaluation of the degree of lift produced by MFU-V, 3D images were taken to measure the reduction in submental area. Oni and colleagues' previous study evaluating MFU-V for submental lift utilized a reduction of >20 mm^2 to indicate a quantitative improvement in submental laxity that translates to visible clinical improvement.[13] Both treatment groups in our trial showed robust submental lift according to prior standardized metrics of improvement with a mean lift of 55.52 mm^2 ± 80.60 from baseline to month 6 for the standard group and 36.15 mm^2 ± 58.10 from baseline to month 6 for the custom treatment group. Our evaluation of submental lift from both a quantitative and qualitative perspective ensures measurement of device efficacy translates to real world improvement in order to produce high patient satisfaction.[14,15]

We saw a statistically significant 1-point improvement in jawline contour using the Merz Jawline Scale in both standard and custom treatment groups, an endpoint that has never been evaluated in prior MFU-V studies. Our study demonstrates

comparable improvement in jawline contour when compared with calcium hydroxylapatite and hyaluronic acid filler for jawline augmentation. Moradi and colleagues' recent study evaluating the effectiveness and safety of calcium hydroxylapatite with lidocaine for improving jawline contour defined treatment response as a ≥1-point improvement in jawline contour according the Merz jawline scale, with a treatment response rate of 75.6% for the treatment group and 8.8% for the control group at week 12.[16] Green and colleagues recent pivotal study evaluating VYC-25L for jawline contour demonstrated ≥1 improvement at 6 months in jawline contour in 68.5% of subjects according to the Allergan Loss of Jawline Definition Scale.[17] Our results showing at least a 1-point improvement in jawline contour indicate clinically relevant results as it is a standard metric used for aesthetic medicine clinical trials to indicate meaningful improvement.[16,18-22]

The I-GAIS at month 6 was statistically significant for greater improvement for the custom group compared with the standard group. Possible reasons for the slightly greater improvement noted by the blinded investigator at month 6 may be due to differences in BMI among standard and custom treatment groups. BMI of subjects was not recorded in our study; however, in Oni and colleagues' study evaluating MFU-V for skin laxity and tightening of the lower face, reviewer assessed global aesthetic improvement increased when 11 of the 93 subjects were excluded from data analysis due to having a BMI >30 kg/m^2.[13] We do know that those of lower BMI, who are greater than 40, have SMAS and platysma at more superficial planes, such as 3.0 mm based on ultrasound imaging in 150 live patients performed by Casabona and colleagues.[9,23] Perhaps those in the custom treatment group demonstrated slightly better I-GAIS due to having a lower BMI which may equivocate to their SMAS/platysma and fibrous septae being located at a more superficial depth. Future studies with a larger sample size could increase the power of our study.

Importantly, S-GAIS and subject satisfaction scores for both treatment groups indicated the majority of patients appreciated a high degree of improvement in the appearance of their lower face and neck. Both standard and custom protocol treatments were well tolerated, and no adverse events occurred.

The seven subjects who were lost to follow up occurred during the COVID-19 lockdowns. The three subjects who withdrew consent were due to compliance related issues. One subject was excluded from three-dimensional data analysis due to poor positioning during photography.

CONCLUSION

This trial emphasizes the importance of visualization with ultrasound to confirm all coagulation points are delivered, so optimal energy gets transferred to tissue and to create a custom treatment protocol for the patient's unique anatomy to maximize results and patient satisfaction. MFU-V is a powerful tool to significantly improve jawline contour which is crucial for optimizing dynamic three-dimensional facial rejuvenation.

DISCLOSURES

This study was funded by Merz North America Inc. Dr Sabrina Fabi is an investigator and consultant for Merz North America Inc. The other authors have no additional relevant disclosures.

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Effectiveness and Safety of a New Hyaluronic Acid Injectable for Augmentation and Correction of Chin Retrusion

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ABSTRACT

Background: A hyaluronic acid (HA) filler intended for non-surgical improvement of chin appearance should ideally be of high strength/firmness (high G') to allow for deep injections on the bone. HA_{SHA} (Restylane® Shaype™) is a new hyaluronic acid (HA) injectable with high G' and high HA concentration (25 mg/mL), engineered by the new NASHA-HD™ (High Definition) technology. HASHA is suitable to be placed periosteally, aiming to mimic the natural shape of the bony chin. This pivotal clinical investigation evaluated effectiveness and safety of HA_{SHA} for augmentation and correction of chin retrusion.

Methods: Subjects ≥18 years with mild or moderate chin retrusion by the Galderma Chin Retrusion Scale (GCRS), were randomized 3:1 to HA_{SHA} (n=103) or no treatment (n=37). Assessments included GCRS (blinded evaluator), aesthetic improvement (Global Aesthetic Improvement Scale [GAIS]), subject satisfaction, and safety.

Results: GCRS responder rate (≥ 1-grade improvement from baseline) was significantly higher for HA_{SHA} (83.3%) vs controls (10.8%) at month 3 (P<0.001), and maintained through month 12 (P<0.001). Aesthetic improvement was high throughout the study in the HA_{SHA} group, according to investigators (≥97%) and subjects (≥89%). Overall, subject satisfaction was high at month 3 and maintained at month 12. Product- or injection-related adverse events were mostly mild or moderate and transient. No product- or injection-related serious adverse events were reported.

Conclusions: HA_{SHA}, a new NASHA-HD™ injectable with extra strength/firmness, was safe and effective for chin augmentation and correction of chin retrusion, with high aesthetic improvement and subject satisfaction throughout 12 months.

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INTRODUCTION

The shape, projection, and profile of the chin are important components of facial attractiveness in both men and women. Chin retrusion may be perceived as less attractive and associated with a desire for chin correction or elongation.[1] Procedures for enhancing chin appearance include surgical procedures, such as permanent alloplast implants (eg, silicone) bony osteotomy, autologous fat transplant, and non-surgical alternatives, such as different types of dermal fillers (eg, silicone, calcium hydroxylapatite, and hyaluronic acid (HA) fillers).[2-4] For patients seeking a minimally invasive and reversible option, HA fillers have shown high patient satisfaction and low risk of severe complications.[5] In addition to a favorable safety profile, filler treatments offer fast recovery[3, 6], and the flexibility to tailor treatments to meet individual needs, including changes in appearance due to aging. Even though the global market offers a wide variety of HA fillers with different physicochemical and rheological characteristics, there remains a need for a strong/firm HA injectable that mimics the natural shape of the bony chin.

NASHA® technology utilizes minimal modification and mild processing that preserves the long natural HA chains, resulting in strong/firm products with high G' (an indicator of strength/

firmness). The NASHA products are Restylane® (Galderma, Uppsala, Sweden) with a G' of 701 Pa (0.1 Hz) and Restylane® Lyft™ (Galderma) with a G' of 799 Pa (0.1 Hz). A new HA injectable, Restylane® Shaype™ (HA_{SHA}; Galderma), has been developed for lower face shaping and to be injected on bone. HA_{SHA} uses the new NASHA-HD™ (High Definition) technology, an evolution of the NASHA platform, using the same low modification and mild processing as NASHA but with increased efficiency of the crosslinking process.This results in HA_{SHA} being an even stronger/firmer product (G' of 916 Pa [0.1 Hz]) with high HA concentration (25 mg/mL). In addition, it is a stable product with high resistance to degradation by heat.

Here, we report the results from a pivotal clinical investigation evaluating the effectiveness and safety of HA_{SHA}, compared to a no-treatment control, for augmentation and correction of retrusion in the chin region.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, evaluator-blinded, no-treatment controlled, parallel-group, multicenter study, conducted at nine centers in Canada, between January 2021 and June 2022. Subjects were healthy men or non-pregnant women aged ≥18 years, with mild (Grade 1) or moderate (Grade 2) chin retrusion at baseline, as assessed by a treatment-blinded evaluator using the Galderma Chin Retrusion Scale (GCRS, where Grade 0 = none, Grade 1 = mild, Grade 2 = moderate, and Grade 3 = severe retrusion). Exclusion criteria included a history of multiple or severe allergies, known or previous allergy/hypersensitivity to local anesthetics; prior procedures in the lower facial region (eg, surgery, permanent/semi-permanent implants); HA or collagen filler treatments in the lower face within the last 12 months; energy-based aesthetic procedures (eg, lasers), mechanical or chemical procedures, botulinum toxin, or cryotherapy in the lower face within the last 6 months; deoxycholic acid treatment in the submental region within the last 6 months; the presence of disease or lesions near the area to be treated (eg, inflammation, infections, acne, psoriasis, scars, cancer or precancer); other underlying conditions (eg, HIV or bleeding disorders) or recent or concomitant medications (eg, anticoagulants, immunosuppressants, chemotherapy, topical facial or systemic corticosteroids) that could expose the subject to undue risk. The study was approved by the Institutional Review Boards at each site and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All subjects provided written, informed consent before starting the study.

Treatment and Follow-up

Subjects were randomized (3:1) to either HA_{SHA} (Restylane Shaype, Galderma, Uppsala, Sweden) injection with the initial treatment given on Day 1 or no-treatment control. HA_{SHA} gel (25 mg/mL HA plus 3 mg/mL lidocaine hydrochloride) was administered using a 1 mL syringe with a 27-gauge, ¾ -inch, ultra-thin wall needle into the chin and surrounding regions. The injection was made into the deep subcutaneous tissue or supraperiosteal plane, as chosen by the treating investigator, with additional local anesthetic if needed. On day 1, subjects received up to 4 mL HA_{SHA} for optimal retrusion correction, defined as ≥1-point improvement from baseline on the GCRS and the best correction that could be achieved (investigator and subject agreement). An optional touch-up treatment with up to 2 mL HA_{SHA} was allowed at month 1, if necessary to obtain optimal aesthetic improvement of the chin. Post-treatment procedures included gently massaging the treated area, applying an ice pack, and providing subjects with guidance on standard post-treatment care. Subjects were followed for up to 12 months from baseline. Subjects in the control group were offered HA_{SHA} treatment at the month 12 visit; where accepted, these subjects were followed for one month after injection.

Assessments

The primary objective was to demonstrate the superiority of HA_{SHA} vs no-treatment control for augmentation and correction of chin retrusion, using Blinded Evaluator live assessment of responder rate at month 3 post-baseline. Subjects were considered responders if they had ≥1-point improvement from baseline on the GCRS.

The secondary objectives were to assess effectiveness and subject satisfaction up to month 12 after treatment. These included Blinded Evaluator-assessed GCRS responder rates, investigator- and subject-assessed aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS; a 7-point scale ranging from "very much worse" to "very much improved"), and a subject-completed Satisfaction Questionnaire. Subjects also completed a 4-week diary, starting on the day of the initial or touch-up treatment, which included documenting the time in hours from injection until they felt comfortable returning to social engagements, and the occurrence of the following predefined, expected post-treatment events (bruising, redness, pain, tenderness, itching, or swelling in the treated area; rated as tolerable, affecting daily activities, or disabling). Investigator-reported safety included documentation of adverse events (AEs) and physical examinations evaluating changes in hair growth in the chin region throughout the study.

Statistical Analysis

A sample size of 140 subjects (randomized 3:1 to HA_{SHA} or no treatment) based on a power calculation was needed to achieve approximately 90% power to demonstrate a difference between groups, assuming GCRS responder rates of 70% in the HA_{SHA} group and 35% in the no-treatment control group, using a two-sided significance level of 0.05.

All effectiveness analyses were performed in the intent-to-treat (ITT) population (all randomized subjects) and safety was assessed in the safety population (all treated subjects or those randomized to the control group). In the primary analysis, GCRS responder rates at month 3 from baseline were compared using Fisher's exact test and presented as estimated responder rates, with two-sided 95% confidence intervals (CI) and *P*-value. Missing data at month 3 were imputed using the Baseline Observation Carried Forward method for the primary analysis. The difference in responder rates was calculated using the Wald Approximation with a continuity correction. A value of $P<0.05$ for the treatment difference was considered significant. The same analysis method was used for the secondary endpoint of GCRS responder rates at months 6, 9, and 12, except that analyses were performed on observed cases (no imputation of missing data). For the GAIS, a responder was defined as a subject with a rating of at least "improved". The time until subjects felt comfortable returning to social engagement was analyzed using Kaplan-Meier methods. All other variables were analyzed descriptively. Post-hoc analyses of responder rates and safety profiles were conducted with stratification by total injection volume (> or ≤ median volume). Statistical analyses were performed using the SAS 9.4 software.

RESULTS

Subjects and Treatment

In total, 140 subjects were randomized to HA_{SHA} (n=103) or no-treatment (n=37) and comprised the ITT population. One subject randomized in error to HA_{SHA} was not treated; 89% completed the study. The most common reasons for withdrawal were subject loss to follow up (6.4%) and withdrawal of consent (2.9%). At Month 12, 25 subjects in the no-treatment group chose to receive HA_{SHA} and these were included in the safety analysis.

Demographic and baseline characteristics were generally similar between the two groups (Table 1). Most subjects were female (97%) and white (84%) and the mean age was 42.0 years (range: 21 to 67). The most common Fitzpatrick skin types were III (46%), II (24%) and IV (24%). All subjects had GCRS Grade 1 or 2 chin retrusion at baseline.

The volume (mean±standard deviation) of injected product for the HA_{SHA} group was 2.10±0.85 mL at initial treatment (N=102) and 0.99±0.55 mL at touch-up treatment (N=73), with a total injected volume of 2.81±1.20 mL. The median (range) total injected volume was 2.80 (0.70, 6.00) mL. The most common injection depth at initial treatment in the HA_{SHA} group was supraperiosteal (98%) and the most common injection method was bolus (76%).

TABLE 1.

Demographics and Baseline Characteristics		
Demographic/Characteristic	HA_{SHA} (n=103)	No Treatment (n=37)
Age (years), mean (SD)	42.3 (12.86)	41.1 (12.54)
Female, n (%)	99 (96.1)	37 (100)
Race[a], n (%)		
White	85 (82.5)	32 (86.5)
Black or African American	2 (1.9)	0
Asian	11 (10.7)	5 (13.5)
Other	10 (9.7)	3 (8.1)
Ethnicity, n (%)		
Hispanic or Latino	3 (2.9)	1 (2.7)
Not Hispanic or Latino	100 (97.1)	36 (97.3)
Fitzpatrick skin type, n (%)		
I	4 (3.9)	0
II	26 (25.2)	8 (21.6)
III	45 (43.7)	20 (54.1)
IV	24 (23.3)	9 (24.3)
V	3 (2.9)	0
VI	1 (1.0)	0
Blinded Evaluator GCRS score, n (%)		
0	0	0
1	56 (54.4)	14 (37.8)
2	47 (45.6)	23 (62.2)
3	0	0

GCRS, Galderma Chin Retrusion Scale; SD, standard deviation
[a]Subjects who selected more than one race were counted once for each race. Totals may add up to over the total number of subjects in the study.

Effectiveness

Improvement in Chin Retrusion (GCRS)

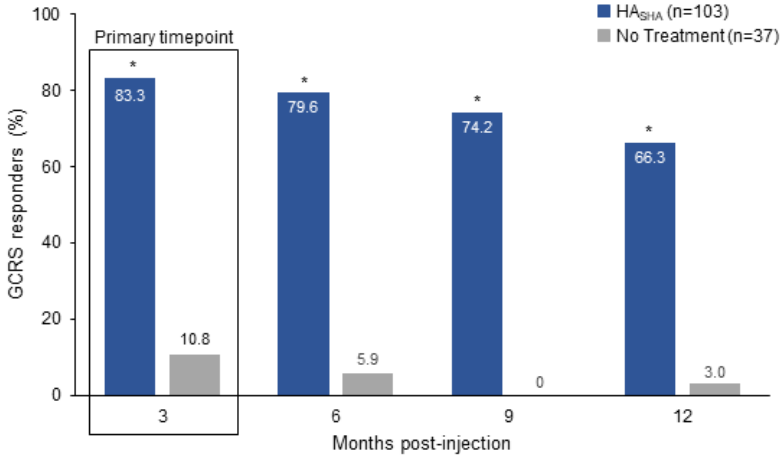
The primary objective to show HA_{SHA} superiority in improving chin retrusion was met. The Blinded Evaluator-assessed GCRS

TABLE 2.

Chin Retrusion Responder Rates[a] at Month 3 Based on the GCRS (ITT population)				
	HA_{SHA}	No Treatment	Difference in responder rate[b] (95% CI)	*P*-value[c]
No.	102	37	--	--
Responders, n (%)	85 (83.3)	4 (10.8)	72.5	<0.001
95% CI, %	74.66–89.98	3.03–25.42	58.34–86.71	--

[a]Responders were defined as subjects with ≥1-point improvement from baseline on the GCRS according to the Blinded Evaluator

FIGURE 1. Blinded evaluator-assessed GCRS responder rates over time (ITT Population).



GCRS, Galderma Chin Retrusion Scale; ITT, intention-to-treat
[a]Responders were defined as subjects with ≥1-point improvement from baseline on the GCRS. At Month 3 (primary endpoint), missing values were imputed using the baseline observation carried forward method. Observed cases are shown for Months 6, 9 and 12. *p<0.001 HA$_{SHA}$ vs no-treatment control, Fisher's exact test

responder rate at month 3 was significantly greater in the HA$_{SHA}$ group compared with the no-treatment control group (83.3% vs 10.8%; *P*<0.001; Table 2). The GCRS responder rate remained significantly greater in the HA$_{SHA}$ group compared with the no-treatment group from month 6 (80% vs 6%; *P*<0.001) through month 12 (66% vs 3%; *P*<0.001) (Figure 1). Subgroup analyses based on injection volume (> or ≤2.8 mL [median volume]) showed similar treatment effects as observed for the full study population (Table 3).

Global Aesthetic Improvement

Aesthetic improvement on the GAIS was achieved in high proportions of subjects, ≥97% and ≥89% as assessed by the treating investigator and subjects, respectively, from month 1 through month 12 after treatment with HA$_{SHA}$ (Figure 2).

Subject Satisfaction

Overall, subject satisfaction was high through month 12, as per the subject satisfaction questionnaire (Figure 3). From month 3 to month 12 post-treatment, subjects in the HA$_{SHA}$ group were satisfied/very satisfied with the shape of their chin (range: 87% to 93%), the projection of their chin (range: 87% to 94%), and their chin profile (range: 82% to 93%). From month 3 to month 12 post-treatment, subjects in the HA$_{SHA}$ group agreed/strongly agreed that their chin looked natural (range: 95% to 96%), made them feel more attractive (range: 71% to 73%), improved their overall satisfaction with their appearance (range: 81% to 92%), and made them feel better about themselves (range: 77% to 79%). A high proportion of subjects who received HA$_{SHA}$ said they would receive the treatment again (range: 80% to 84%) and would recommend the treatment to a friend (range: 92% to 97%).

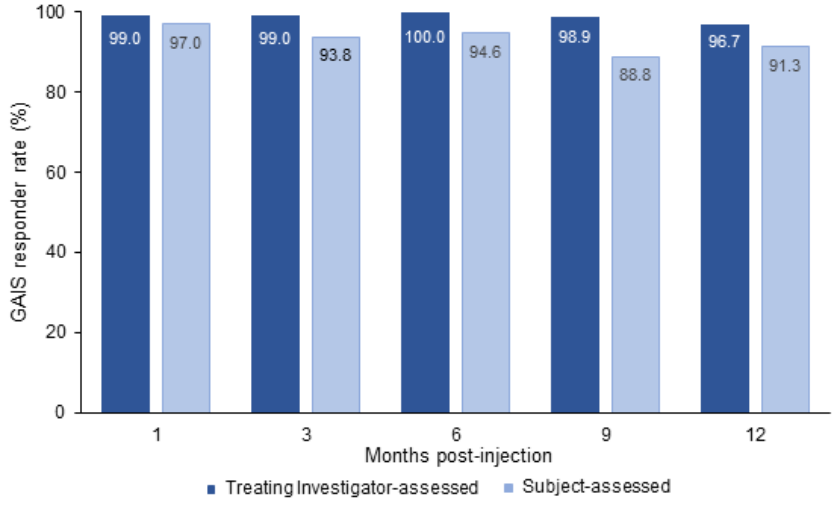
TABLE 3.

Post-Hoc Analysis of Blinded Evaluator-Assessed GCRS Responder Rates and Product- and Injection-Related Adverse Events by HA$_{SHA}$ Total Injection Volume (Including Initial and Touch-Up) ≤2.8 mL and >2.8 mL (Median Total Injection Volume)[a]

	Number of Subjects (m/n)	
	Total Injection Volume ≤2.8 mL (N=53)	Total Injection Volume >2.8 mL (N=49)
GCRS responders[b] at month 3	42/48 (87.5%)	43/48 (89.6%)
GCRS responders[b] at month 6	38/47 (80.9%)	36/46 (78.3%)
GCRS responders[b] at month 9	29/43 (67.4%)	37/46 (80.4%)
GCRS responders[b] at month 12	29/46 (63.0%)	32/46 (69.6%)
	Total Injection Volume ≤2.8 mL (N=53)	Total Injection Volume >2.8 mL (N=49)
Subjects reporting any product-related AEs	7/53 (13.2%)	11/49 (22.4%)
Subjects reporting any injection-related AEs	7/53 (13.2%)	6/49 (12.2%)
Subjects reporting implant site nodule/mass	3/53 (5.7%)	9/49 (18.4%)

AE, adverse event; GCRS, Galderma Chin Retrusion Scale; m=number of subjects with event; n=non-missing subjects
[a]Observed cases among subjects with any (mild or moderate) GCRS score at baseline in the HA$_{SHA}$ group; [b]Defined as a subject with ≥1-grade improvement from baseline on the GCRS

FIGURE 2. GAIS responder rates over time according to Treating Investigator assessment and Subject assessment (ITT population).



GAIS, Global Aesthetic Improvement Scale; ITT, intention-to-treat
[a]The responder rate was defined as the percentage of subjects with a rating of at least "improved" on the GAIS. Month 1 is counted from the last treatment (i.e. from touch-up for those who received a touch-up or from initial treatment for those who did not receive a touch-up). Months 3–12 are counted from baseline.

Return to Social Engagements

The self-reported median time until subjects felt comfortable returning to social engagements was 19.0 hours (95% CI, 5.0, 26.0) after initial treatment and 7.0 hours (95% CI, 2.0, 20.0) after touch-up treatment.

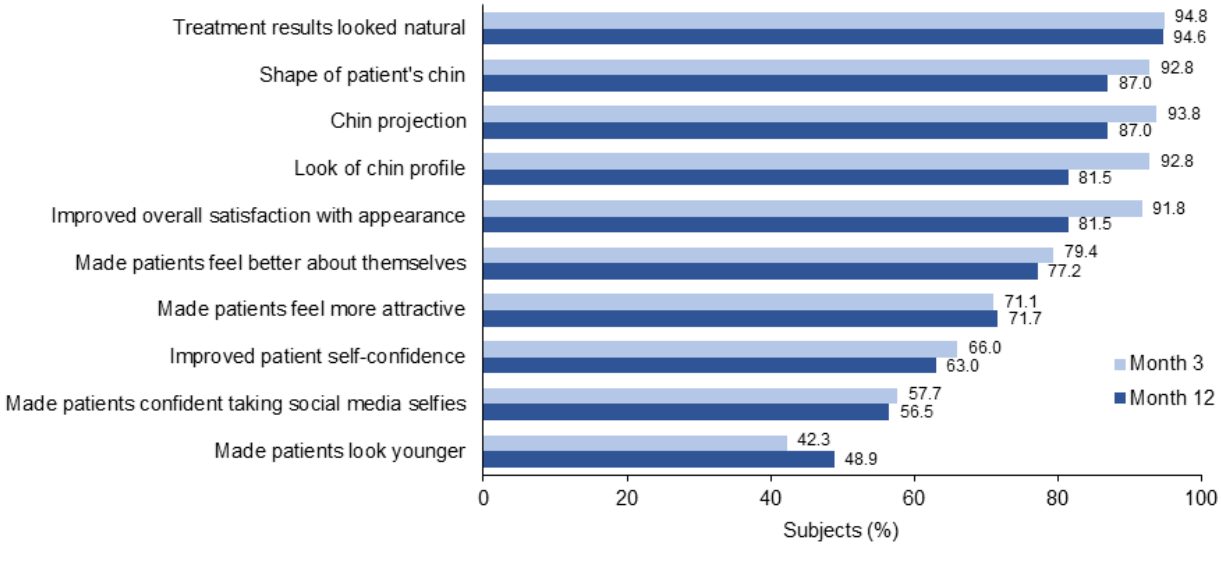
Subject Photographs

Example photographs of a subject before and after treatment with HA_{SHA} are provided in Figure 4.

Safety

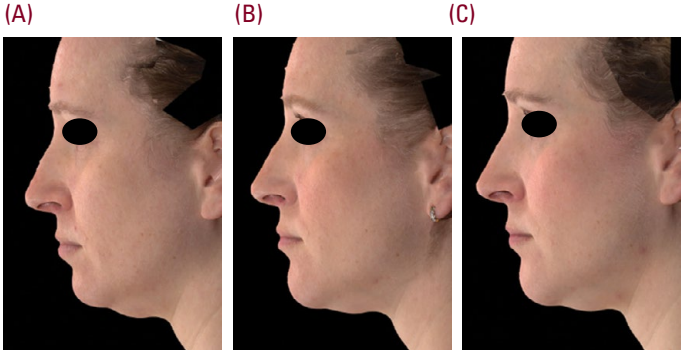
Safety results are reported for all subjects who were injected with HA_{SHA}(N=127), which included 25 subjects from the former control group who chose to receive treatment at month 12. Among the 123 HA_{SHA}-treated subjects who provided information in the 4-week subject diary, 100% reported at least one predefined, expected post-injection event (pain, tenderness, redness, bruising, swelling, or itching) after treatment. The most common diary-reported post-injection events after the initial

FIGURE 3. Subject satisfaction in the HA_{SHA} group at month 3 and month 12 (ITT population).



ITT, Intention-to-treat; The percentage of patients who responded "satisfied" or "very satisfied" or "strongly agree" or "agree" on the Subject Satisfaction Questionnaire.

FIGURE 4. Photographs of a 42-year-old female at baseline, GCRS=2 (A), month 3, GCRS=0 (B), and month 12, GCRS=0 (C). The subject was injected with 2.8 mL HA_{SHA} at initial treatment and with 1.7 mL HA_{SHA} at the 1-month touch-up.



injection were tenderness (99% of subjects), pain (97%), and swelling (95%; Figure 5). Most subjects reported these events as tolerable and as resolved within 1-2 weeks. A similar profile of post-injection events was reported after the touch-up injection (Figure 5).

In total, 24 subjects (19%) treated with HA_{SHA} experienced a product- or injection-related AE, 80% of which were mild or moderate in intensity. The most common product- or injection-related AEs (>2.0% of subjects) were implant site mass (5.5%), implant site pain (4.7%), implant site nodule (3.9%), and headache (3.1%). Implant site pain generally started on the day of injection and had a median duration of 2.0 days. There were 13 events of implant site mass (n=8) and nodules (n=5). Of these, no events of mass and 4 nodules were delayed (starting >21 days after treatment). Two events of nodule were inflammatory, and one of these had delayed onset. There were no product- or injection-related serious AEs reported. No subjects experienced a change in chin hair growth during the study.

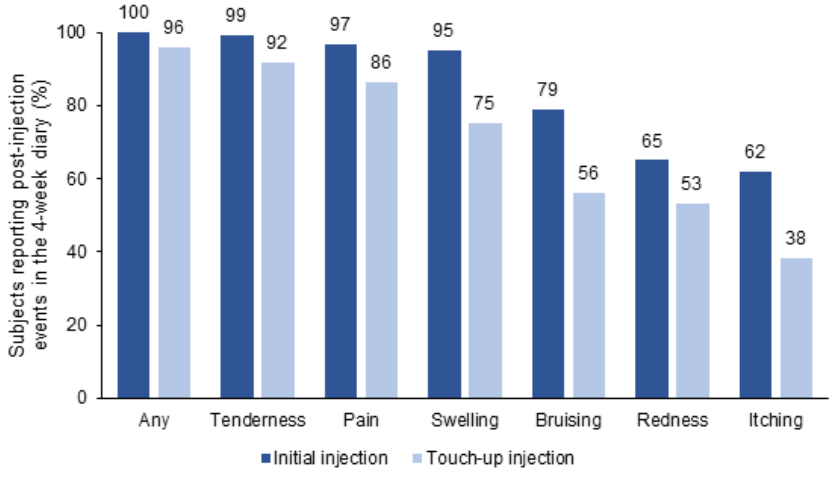
Post hoc analyses of product- or injection-related AEs based on injected volume (> or ≤2.8 mL, the median volume) showed that a larger proportion of subjects had AEs related to the product —including implant site nodules and mass—after injection with >2.8 mL (Table 3).

DISCUSSION

The results of this study demonstrate that HA_{SHA} significantly improves chin retrusion from baseline, compared with a no-treatment control. Notably, the GCRS response (Figure 1) was maintained in the majority of subjects, with a significant difference between the two groups for up to 12 months after the initial injection (with a touch-up at month 1). The long-term improvement in chin retrusion with HA_{SHA} treatment is supported by the GAIS results, which showed a high proportion of individuals (97% investigator assessment, and 91% subject assessment, Figure 2) with aesthetic improvement that was maintained at month 12. Even though not directly comparative, other pivotal studies evaluating chin augmentation with HA-based fillers, eg, using VYC-20L (Juvéderm VolumaXC[â], Allergan) have shown GAIS aesthetic improvement rates for chin augmentation at month 12 of 91%/82% according to investigators/subjects.[7] In a pivotal study of VYC-25L (Juvéderm Volux[â], Allergan) GAIS responder rates in the treatment of chin retrusion were 84%/77% at month 12 according to investigators/subjects, respectively.[8]

HA_{SHA} had an overall acceptable safety profile in relation to the positive results of treatment reported by the subjects, eg, high satisfaction and GAIS results (Figures 2 and 3). Subject-reported, predefined, expected injection-related events (pain, tenderness, redness, bruising, swelling, and itching, Figure 5) in the 4-week diaries were mostly tolerable and transient, usually resolving within 1–2 weeks. Most product- or injection-related AEs reported by the investigators were mild or moderate in intensity

FIGURE 5. Subject diary-reported predefined, expected post-injection events (safety population).



[a]Proportion of subjects reporting post-injection events in the 4-week diary completed after each injection.

and there were no product- or injection-related serious AEs. The most commonly reported product- or injection-related AEs were implant site reactions, mass, pain, and nodules, which were mostly mild or moderate in intensity and resolved during the study. Post-hoc analyses revealed a relationship between total injected volume (initial and touch-up) and product-related AEs, including mass and nodules, with a higher AE frequency with volumes above 2.8 mL (Table 3). The GCRS results tended to be similar for both subgroups (Table 3) indicating that both higher and lower volumes (≤ median and > median) achieved optimal aesthetic results. However, overall, these findings suggest that a smaller total injection volume may be preferable, to reduce the risk of developing nodules or mass. Smaller volumes of product per injection point have previously been reported to minimize the risk of serious AEs.[6] Overall, the safety profile for HA_{SHA} appears to be generally comparable with that reported for other HA fillers injected in the chin area.[7,8] Other pivotal studies have reported injection site mass/nodule rates of 21.8%/1.7% for VYC-25L[8] and 60.2% ('lumps/bumps') for VYC-20L,[7] while our study reported mass/nodule rates of 5.5%/3.9% for HA_{SHA}.

The patient perspective is important in aesthetic treatments, particularly as appearance can impact the perception of attractiveness and potentially psychological well-being.[1,2] Subject satisfaction rates in the HA_{SHA} group remained high throughout the present study (Figure 3). At month 12, most subjects (82 to 87%) remained satisfied/very satisfied with the shape, projection, and profile of their chin, as well as their overall appearance. Most subjects still felt after 12 months that the treatment results looked natural (95%), and made them feel more attractive (72%) and better about themselves (77%).

CONCLUSION

The results of this study showed that HA_{SHA} is safe and effective for chin augmentation and improvement of chin retrusion, with high aesthetic improvements and high subject satisfaction lasting through 12 months. The study findings support HA_{SHA} as a safe option for patients with mild to moderate chin retrusion (by GCRS) looking for a minimally invasive and reversible treatment option for chin augmentation.

DISCLOSURES

Andreas Nikolis is a paid consultant, speaker, and clinical trial investigator for Galderma, Allergan, Prollenium, and Merz. Vince Bertucci is a paid consultant, speaker, and/or clinical trial investigator for Galderma, Allergan Aesthetics, an AbbVie Company, Clarion, Cutera, Merz, Prollenium, Revance and Teoxane. Shannon Humphrey is a speaker, consultant, and/or investigator for Galderma, Merz, Revance, and Allergan Aesthetics, an AbbVie company. Jason K Rivers is an advisory board member, speakers' bureau member, and investigator for AbbVie/Allergan; advisory board member and paid consultant for Bausch Health; Investigator for Galderma; advisory board member, speakers' bureau member, paid consultant, and investigator for Leo Pharma; investigator for Medytox; consultant for MetaOptima Technology Inc; investigator for Pfizer; investigator for SaNOtize; founder, stockholder of Riversol Skin Care Solutions Inc. Nowell Solish is a clinical trial investigator for Galderma. Andrei Metelitsa is a paid consultant, speaker, and clinical trial investigator for Galderma and Allergan. Nathan Rosen is a clinical trial investigator for Galderma. Kristy Bailey is a clinical trial investigator for Galderma. William McGillivray is a clinical trial investigator for Galderma. Annika Rugheimer, Felipe Weinberg, Torun Bromée, and Inna Prygova are employees of Galderma.

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ORIGINAL ARTICLE

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The Two-Stage Folded Paramedian Forehead Flap Without Cartilage Grafts for Full Thickness Distal Nasal Defects: A Review of 35 Patients

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ABSTRACT

Background: Full thickness defects of the ala, soft triangle, and nasal tip involving the nasal lining have traditionally been repaired with the three-stage folded paramedian forehead flap (FPFF), with a cartilage graft for support. For similar defects, the authors utilize the two-stage FPFF without cartilaginous support which provides reproducible functional and aesthetic results.
Objective: To describe the authors' experience with the two-stage FPFF, including outcomes, complications, and design modifications to enhance functional and aesthetic success.
Methods: An IRB-approved retrospective database review of FPFF was performed at two sites. Using postoperative photographs, outcomes were assessed by blinded non-investigator dermatologist raters using a modified observer scar assessment scale.
Results: Thirty-five patients were reconstructed using the two-stage FPFF without cartilage grafts. Subjective assessment of scar vascularity, pigment, relief, and thickness by 3 independent reviewers yielded an overall cosmesis score of 8.4±1.9 (out of 40).
Conclusion: The two-stage FPFF without cartilage grafts is a reliable, cosmetically elegant repair that can provide optimal functional and aesthetic results for complex unilateral distal nose defects.

J Drugs Dermatol. 2024;23(4):262-267. doi:10.36849/JDD.7358

INTRODUCTION

A workhorse for full thickness nasal defects is the folded paramedian forehead flap (FPFF) owing to its ideal color, size, and texture, and its ability to restore cover, lining, and support. Even small defects that compromise the alar rim and involve the nasal lining and mucosa are challenging to reconstruct. It is vital to maintain the integrity of nasal mucosa because failure to do so can lead to fibrosis and stenosis of the nasal airway. Of utmost importance is maintaining the patency of the nasal valve to preserve inspiratory function.

Replacing the lining is often tedious because of the poor visibility and surgical access. There are several traditional options to replace nasal lining during reconstruction, which often depend on the size and location of the defect.[1,2] Small defects no more than a few millimeters can be closed primarily.[2] Other options include hinge-over flaps, a second local flap (nasolabial flap or second forehead flap), a prelaminated and prefolded forehead flap,[3] support grafts (composite skin graft or full thickness skin graft), intranasal lining flaps ("bucket-handle flap"), microvascular distant flaps, and the FPFF (traditionally three stages) in which the flap folds the forehead onto itself to line the nostril rim.[1,2,4,5] However, hinge-over flaps have unpredictable vascularity, may occlude the airway, are difficult to mold with cartilage grafts, and may not survive if longer than 1.5 cm.[6-7] A second local flap adds additional facial scars. A composite skin graft has variable survivability but can provide cover and lining for defects < 1.5 cm in size.[1] A skin graft by itself cannot provide primary support because it must be placed against the flap's vascular bed to survive. The prelamination (prefabrication) technique is elegant but offers extreme technical mastery and cartilage harvesting. Lastly, skin from distant flaps does not match facial skin quality.

Besides the FPFF, there are limited reconstructive options that will give satisfactory results in nasal defects larger than 1.5 cm that also require replacement of support or lining. A two-stage nasolabial interpolation flap or a Spear flap could be considered for a deep alar defect involving mucosa but is less commonly

used for a defect larger than 2 cm or also involving the nasal tip or dorsum. If a defect requires support replacement or lining, the FPFF is ideal.

We describe the two-stage FPFF without the use of cartilage grafts to repair full-thickness distal nasal defects. This technique reduces the morbidity of prolonged 6-weeks of a three-stage PFF, without compromising cosmetic or functional outcomes and will be described in detail.

Surgical Technique

- Patients with unilateral full-thickness defects of the nasal ala and/or soft triangle are excellent candidates for this procedure (Figures 1 and 2).
- Tissue quality of the forehead must be evaluated first for any abnormalities, new cancers, scars from previous surgeries, or contour irregularities which may preclude its use.
- An ipsilateral, vertical PFF is preferred as its low pivot point provides easy flap reach to the defect without transferring hair-bearing scalp. A narrow pedicle should be less than 1.5 cm as this may permit primary closure of the forehead.
- Based on the exact size and shape of the defect (a template can be used) the flap body is created. A lining flap can be drawn as an extension of a full thickness forehead flap (the area normally discarded as a standing tissue cone of a PFF donor site). Inclusion of scalp hair is avoided for the portion of the flap that will become nasal rim and ala, but hair-bearing scalp skin can be included for the portion of the flap that is used to replace the nasal mucosa lining, as this can help limit postoperative rhinorrhea.
- Ensure the flap is the appropriate length to reach the defect by placing a piece of gauze at the pedicle's pivot point at the medial brow and moving it to the defect.
- The incision is made superficially at the distal portion of the flap while tracing the template. Sharp (scalpel) undermining is performed to release the flap from the underlying tissue. The undermining plane is critical - the body of the flap that will be sutured into the defect should be undermined at the dermo-pannicular junction, to include the medium-sized vessels found at this level. The proximal incision and undermining plane can then immediately deepen to the periosteum once the body of the flap is undermined so that the pedicle is robust.

FIGURE 1. (A) 2 x 1.3 cm full-thickness defect of the ala, sidewall, and medial cheek. Cheek advancement was performed to close the medial cheek portion of defect. (B) Swimmer's view. Intraoperative folded forehead flap. (C) Lateral view. Intraoperative medial cheek advancement performed prior to the folded forehead flap. (D) 36-week follow-up showing appropriate alar contour

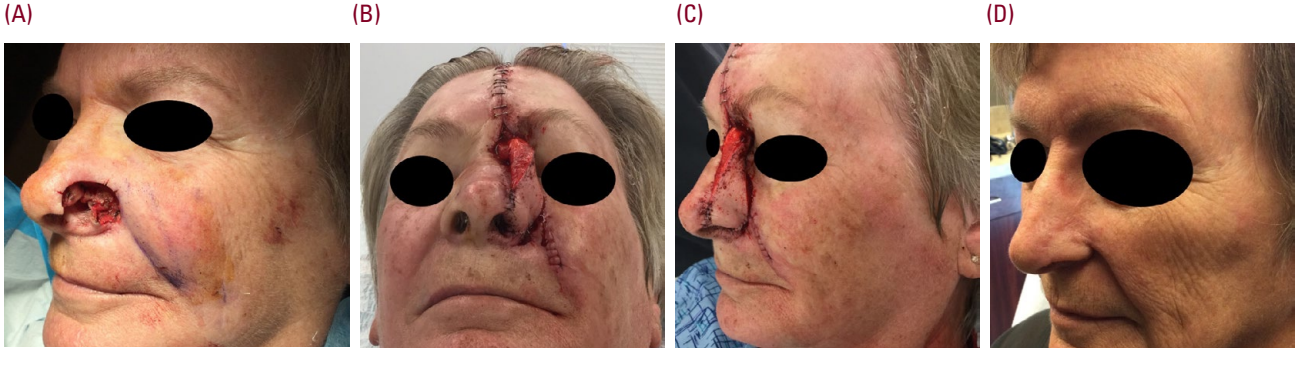


FIGURE 2. (A) 2.6 x 1.5 cm defect of the nasal ala and sidewall. (B) Swimmer's view. Intraoperative folded forehead flap. (C) Frontal view. Intraoperative folded forehead flap. (D) 34-week follow-up showing appropriate alar contour after post-operative dermabrasion.

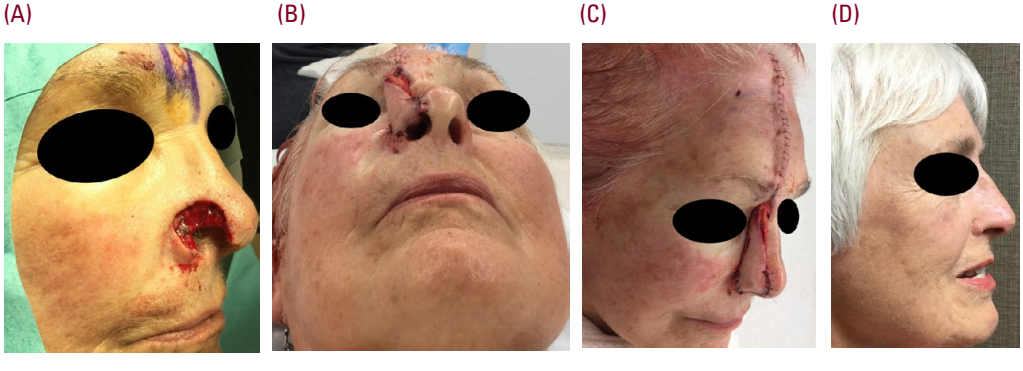


FIGURE 3. (A) 2.1 x 2.1 cm full-thickness defect of the nasal tip and soft triangles. (B) Swimmer's view. Intraoperative folded forehead flap. (C) Frontal view. Intraoperative folded forehead flap. (D) 48-week follow-up showing appropriate nasal projection and recapitulation.

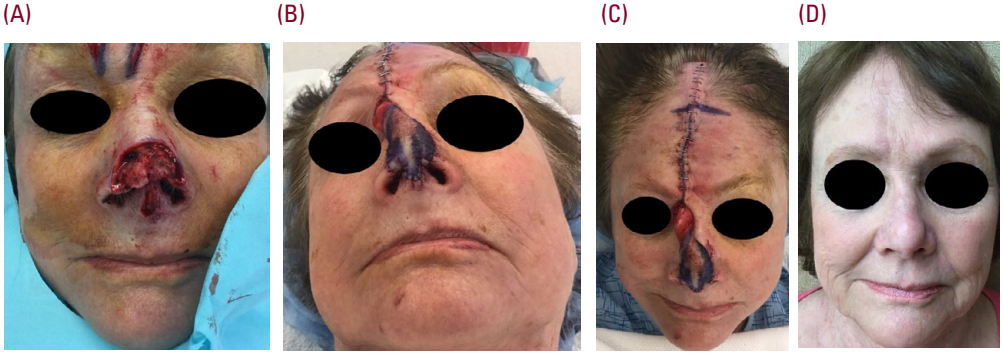
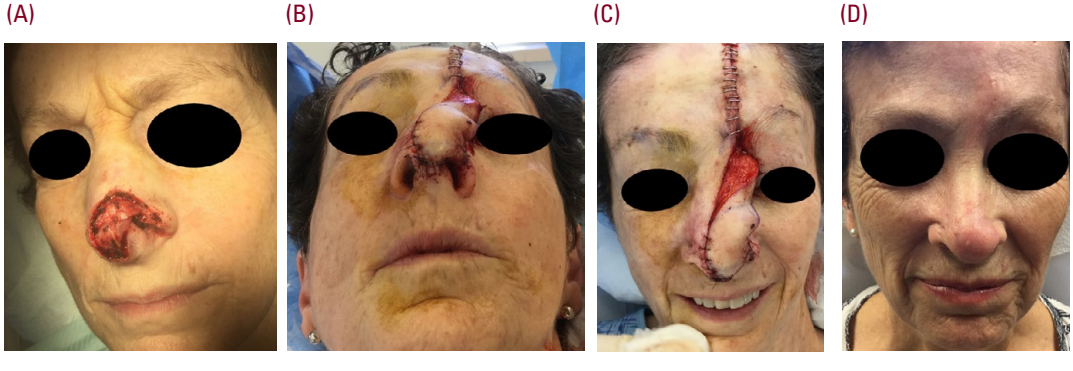


FIGURE 4. (A) 3 x 2.6 cm full-thickness defect of the nasal tip, soft triangles, ala, and columella. (B) Swimmer's view. Intraoperative folded forehead flap. (C) Frontal view: Intraoperative folded forehead flap. (D) 21-week follow up showing recapitulation of the distal nose.



- Further thinning of the distal portion of the flap is performed to remove any excess subcutaneous tissue. Thinning is performed akin to an FTSG, but an aforementioned small amount of subcutis is still retained to preserve the vascular plexus found at the dermo-pannicular junction.
- Light cauterization can be performed on any actively bleeding vessels.
- The flap is sutured into place, starting with the nasal lining. Absorbable sutures are used when suturing the nasal lining (5-0 polyglactin 910 or 5-0 chromic gut).
- No primary cartilaginous support is placed within the folded area.
- The more proximal portion of the flap body is then folded back on itself to supply the nasal surface and is sutured into place using nonabsorbable sutures (6-0 Ethilon). This is done with interrupted, transcutaneous sutures only. Close the donor area on the forehead starting proximally. The distal end of the flap can heal by the second intention if tension prevents primary closure.
- A nasal trumpet is placed to sandwich the two undersides of the flap together to increase adherence and possibly decrease the risk of hematoma. It also acts to stent the nostril open and promotes healing from a 3-dimensional structural standpoint. It is left in for a total of two weeks (a new nasal trumpet is placed at the 1-week bandage change follow up).
- Three weeks later, the second stage involves flap take-down. Only a small proximal portion of the flap, if any, is thinned and set in, as aggressive thinning had already been done in the first stage.

MATERIALS AND METHODS

An IRB-approved retrospective review was performed at 2 sites to identify all patients with surgical defects of the distal nose involving the nasal lining who underwent a two-stage FPFF without cartilage grafts between July 2017 and July 2021. All reconstructions were performed by 2 fellowship-trained Mohs surgeons with at least 3 years of experience, and final cosmetic outcomes were assessed at a minimum of 6-months post-

operatively. Outcomes were assessed based on image review by 3 board-certified non-investigator dermatologists. These reviews were blinded, and the case order was randomized using an open access web-based randomization tool.[9]

A modified Observer Scar Assessment Scale (OSAS) was used to account for the retrospective nature of the analysis.[10,11] Each scar was graded on 4 parameters including vascularity, pigmentation, thickness, and relief. Pliability was omitted, as it was felt that this could not be accurately assessed through image review. Individual parameters receive a score of 1-10 from each reviewer, 1 being normal skin and 10 being the worst imaginable scar. Collective scores range from 4-40, 4 being normal skin and 40 being the worst imaginable scar.

Surgical complications were assessed through chart review for each patient and included short-term (bleeding, infection, dehiscence, and necrosis) and long-term outcomes (alar displacement and altered nasal valve function). In addition, the need for additional revision procedures following the two-stage FPFF is also reported. All reviewer and outcomes data was compiled and analyzed using Microsoft Excel and SAS and mean and SD were reported for final cosmetic outcomes for each parameter.

RESULTS

A total of 35 patients (54% male) met the criteria and were included in the final assessment. Each of the included surgical defects involved nasal lining or mucosa, and the nasal ala, soft triangle, and nasal tip were the most common subunits involved. Other affected subunits included the nasal sidewall, columella, nasal dorsum, medial cheek, and upper cutaneous lip (Table 1). The defects ranged in greatest diameter from 0.6 to 3.6 cm (2.02±0.72), and all were closed with transposed skin from the ipsilateral side of the defect.

No major complications were noted following these procedures including flap necrosis, dehiscence, infection, alar displacement, or altered nasal valve function. Three patients noted minor bleeding after surgery. Three patients were bothered by the decrease in the size of the external valve opening, but none of these cases led to functional impairment and they did not seek correction. Two patients had minor scar revisions to redefine the alar sulcus a few months after surgery. Postoperative manual dermabrasion was performed in 5 patients to resolve step-offs, and 1 patient was treated with intralesional triamcinolone to lessen flap bulkiness (Table 2).

OSAS ratings for 35 patients are summarized in Table 3. Blinded observers gave the two-stage FPFF an overall average cosmesis score of 8.4±1.9 (out of a possible 40). Pigmentation (1.80±0.71 out of 10) and vascularity (1.89±0.84 out of 10) received the lowest individual scores. In comparison, relief (2.35±1.17 out of

TABLE 1.

Patient Data	
Characteristic	**Value**
Age, median (range)	74 (53-89)
Surgical defect size x, median (range), mm	20 (6-36)
Surgical defect size y, median (range), mm	17 (10-36)
Surgical location, n	
Nasal tip	18
Soft triangle	22
Nasal ala	32
Columella	5
Nasal dorsum	3
Nasal sidewall	16
Upper cutaneous lip	1
Medial cheek	4
Location of pedicle in relation to defect, n	
Ipsilateral	35
Contralateral	0
Cartilage graft, n	
Cartilage graft	0

TABLE 2.

Revisionary Procedures and Complications	
Revision or Complication	**n (%)**
Complication	
Total flap necrosis	0 (0)
Superficial flap necrosis	0 (0)
Post-op infection	0 (0)
Altered nasal valve function	0 (0)
Nasal valve cosmesis*	3 (9)
Dehiscence	0 (0)
Hematoma	0 (0)
Minor bleeding after surgery	3 (9)
Revisionary Procedure	
Scar revision	2 (6)
Dermabrasion	5 (14)
Laser therapy	0 (0)
Intralesional Kenalog	1(3)

*Patient bothered by diminished size of external nasal valve opening

TABLE 3.

OSAS Scores						
Patient	Average Vascularity	Average Pigmentation	Average Thickness	Average Relief	ATS	SD for ATS
1	1.3	2.0	1.7	2.0	7.0	0.8
2	1.7	1.7	3.0	2.0	8.4	1.7
3	2.0	1.7	2.3	1.7	7.7	2.9
4	3.0	2.3	2.3	1.7	9.3	3.4
5	1.3	1.3	1.7	2.3	6.6	2.5
6	2.3	2.0	2.3	3.0	9.6	4.1
7	1.3	1.3	1.3	1.3	5.2	1.9
8	2.0	1.7	3.7	3.0	10.4	2.1
9	1.3	1.7	3.3	3.7	10.0	1.6
10	1.3	1.3	1.3	1.3	5.2	1.9
11	1.7	2.0	3.0	3.7	10.4	4.2
12	1.3	1.7	1.7	2.0	6.7	3.1
13	1.3	1.7	2.0	2.3	7.3	4.0
14	3.3	2.0	3.3	2.0	10.6	1.7
15	1.7	1.7	3.0	3.0	9.4	1.9
16	2.0	2.7	2.0	2.3	9.0	2.2
17	1.7	1.7	2.7	1.7	7.8	1.9
18	2.0	1.7	2.0	1.7	7.4	2.9
19	2.3	2.0	3.3	3.0	10.6	0.9
20	1.0	1.3	1.3	1.3	4.9	0.8
21	2.3	2.3	3.0	1.7	9.3	3.6
22	1.7	1.3	2.0	2.0	7.0	1.6
23	2.3	2.0	2.7	3.3	10.3	2.1
24	2.0	1.7	1.3	1.3	6.3	1.7
25	1.0	1.0	2.7	2.7	7.4	2.1
26	1.3	1.7	2.7	3.0	8.7	1.9
27	1.3	1.7	3.0	3.0	9.0	2.2
28	1.0	1.0	1.0	1.7	4.7	0.5
29	1.0	1.0	1.7	2.0	5.7	1.2
30	1.7	2.0	3.3	2.7	9.7	1.2
31	3.0	3.3	2.3	3.0	11.6	4.1
32	2.7	2.0	2.0	2.0	8.7	1.9
33	2.0	2.3	2.7	2.7	9.7	2.4
34	2.0	2.0	3.3	2.3	9.6	0.9
35	2.0	2.3	3.3	4.0	11.6	0.9
Total Average	1.8	1.8	2.4	2.4	8.4	2.1

ATS - Average total score
SD for ATS – Standard deviation for average total score

TABLE 4.

OSAS Observer Agreement Data			
Parameter	3/3 Agree	2/3 Agree	0/3 Agree
Vascularity	7	20	8
Pigmentation	10	23	2
Thickness	2	22	11
Relief	2	17	16

10) and thickness (2.41±1.12) also received relatively low scores. Agreement among raters was relatively good (Table 4).

DISCUSSION

This two-stage FPFF involves aggressive thinning of the distal portion of the flap to avoid bulkiness, an additional stage, and further revisions. None of our patients experienced necrosis from aggressive thinning, nor functional inspiratory deficits from excess bulkiness of the external nasal valve opening, although three were concerned about the cosmetic appearance of it being slightly diminished in size. Additionally, the folded flap provides an appropriate framework to negate the need for cartilaginous support. None of our patients experienced functional deficits from lack of support or nasal valve collapse without the use of a cartilage graft. Moreover, not harvesting a cartilage graft may reduce patient morbidity by avoiding another operative site and complications such as perichondritis. As the natural ala lacks cartilage, it is intuitive that cartilage may not be necessary for replacement. Further, a batten graft may result in exaggerated bulkiness and asymmetry.

In contrast, the traditional two-stage FPFF for full thickness defects utilizes cartilage grafts for support. During the initial stage, the PFF is turned over to envelope the cartilage graft. However, it often requires staged revisions to debulk the flap.[11] Because of the purported high metabolic demands of the cartilage graft,[11] the distal portion of the flap is not aggressively thinned during the first stage, and often remains bulky after takedown, thereby requiring further revisions. Conversely, this two-stage FPFF can be aggressively thinned initially because it lacks a metabolically demanding cartilage graft.

The modified 3-stage FPFF described by Menick[3,4] has traditionally been the gold standard for unilateral, full-thickness defects.[4,5] It adds a full-thickness lining extension to the distal end of the covering forehead flap that is folded inward to provide cover and lining. During the second stage, the alar margin is incised, thereby separating the proximal and distal portions of the flap. Excess soft tissue is removed by reelevating the covering flap. Then, structural cartilage graft support is inserted between the folded lining. The covering flap is returned to the defect and divided at a later third stage which finalizes the repair.[1,4,5]

Proponents of the three-stage PFF claim that it is advantageous for large, full-thickness nasal defects and state it results in an enhanced aesthetic outcome.[3,4,11,12] Because the 3-stage approach can tolerate more aggressive thinning of the flap during the intermediate stage (versus the initial stage in the two-stage approach) when the flap has effectively physiologically delayed, proponents argue this allows for more precise 3-dimensional contouring and fine adjustments of cartilage grafts, leading to enhanced cosmetic outcome.[4,5,11,12] We believe this precise 3-dimensional contouring can be accomplished in two stages with FPFF due to aggressive initial stage flap thinning. However, comparative studies between the well-described two and three-stage PFF suggest equivocal aesthetic outcomes.[12-17] A recent review comparing these approaches concluded the three-stage PFF might be advantageous for larger, more complex defects and patients at risk of vascular compromise.[11]

While we have used this approach for large, complex defects with satisfactory results (Figures 3 and 4), it may be best for full-thickness, unilateral defects. For larger, more complex, bilateral defects, additional studies need to be performed. Additional limitations of the current analysis include its retrospective nature with image review. The OSAS is validated for the assessment of scars in person, however, there is a paucity of scoring systems for image-based analyses. We opted to modify the OSAS instead of unvalidated visual analog scales that have been reported in similar studies. Finally, further studies are needed to directly compare outcomes between the 2-stage FPFF without cartilage grafts, the traditional 2-stage FPFF with cartilage grafts, and the modified 3-stage FPFF.

CONCLUSION

This two-stage FPFF without cartilage grafts is a dependable and efficient option for repairing full-thickness unilateral defects of the nose and saves the patient an extra 3 weeks of morbidity compared to the three-stage option. The overall average cosmesis score of 8.4 (out of a possible 40) indicates a good cosmetic outcome. Our results highlight the consistently high cosmetic outcomes achieved by this reconstruction without sacrificing function, and it can be considered in cases that may have previously been reconstructed with the 3-stage FPFF.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Aesthetic Improvement With Topical Body Skin Treatment as a Complement to Cryolipolysis

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ABSTRACT

Background: A firming and toning cosmetic body lotion (FTB) was developed to target key pathways relevant to body skin health and rejuvenation that may complement the improvements observed after noninvasive body contouring (NIBC). A pilot study explored the efficacy and tolerability of FTB as an adjunct to cryolipolysis.

Methods: An open-label, single-site, single-arm, 12-week study enrolled subjects aged 20 to 65 who had pre-elected to receive 1 or more cryolipolysis treatments (CoolSculpting® or CoolSculpting® Elite; Zeltiq Aesthetics, Inc.) on the inner thigh, back/bra fat, or submental areas. Immediately post-procedure, the investigator applied FTB to the treated area. Subjects then applied FTB topically twice daily for 12 weeks on the treated area. Skin texture and firmness were graded visually by the investigator using a 10-point scale, and subjects graded effectiveness, product attributes, and satisfaction with a questionnaire.

Results: Seventeen subjects (16 women, 1 man) enrolled. After 12 weeks of FTB application, significant improvements in skin firmness were observed in all treated areas, while skin texture showed improvements on the inner thigh and back/bra fat (all $P \leq 0.009$). With continued use following cryolipolysis, more than 70% of subjects agreed that FTB improved skin firmness, smoothness, and overall appearance. Subjects indicated that FTB was an effective adjunct to cryolipolysis. Throughout the study, 86% to 92% of subjects reported "fair," "good," or "excellent" satisfaction with FTB.

Conclusion: This pilot study suggests that FTB may complement skin improvements seen post-NIBC.

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INTRODUCTION

In the development of a topical body skin treatment (SkinMedica® Firm & Tone Lotion for Body [FTB]; Allergan Aesthetics, an AbbVie Company, Irvine, CA) to address age-related skin problems, a key focus has been the identification of pathways important to body skin health and rejuvenation that are responsive to modulation by selected botanical preparations.[1] FTB was formulated to target key pathways that contribute to overall skin quality, including improved dermal extracellular matrix integrity, enhanced lymphatic drainage, cellular clearance and recycling, and adipocyte metabolism.[1] FTB was originally conceived and shown to be tolerable and effective in improving body skin quality when applied to the upper arms and thighs.[2] However, the active botanicals identified via this rational treatment approach might also target pathways capable of further improving skin tone evenness, skin firmness, and other aesthetic attributes overlying the skin following noninvasive body contouring (NIBC) procedures.[1]

NIBC techniques that target subcutaneous fat include cryolipolysis,[3] high-intensity focused ultrasound,[4] low-level near-infrared laser lipolysis,[5] and combined high-intensity focused electromagnetic field and radiofrequency lipolysis.[6,7] The use of NIBC techniques continues to grow. Worldwide, an estimated 560,464 nonsurgical fat reduction procedures were performed in 2020, an increase of 29% versus 2016.[8] In the United States, over 1 million body sculpting procedures were performed in 2019.[9] Approximately 26% (257,868) were cryolipolysis, representing a more than 3-fold increase since 2012.[9,10] The popularity of NIBC stems from its ability to deliver fat reduction noninvasively without the need for anesthesia and a faster recovery time compared with invasive liposuction.[11,12]

Cryolipolysis is the process by which controlled cooling extracts heat from subcutaneous tissue to induce selective adipocyte cell death, thereby reducing the thickness of the subcutaneous fat layer.[13-16] There is also clinical evidence of skin tightening and texture improvement in cryolipolysis-treated areas, along with immunohistochemical evidence that neocollagenesis may play a role.[16-19] It is thus also reasonable to assume that further enhancement of the skin appearance can be achieved by applying topical treatments that target multiple relevant processes following cryolipolysis.[1,20]

To characterize the effect of FTB as an adjunct to NIBC procedures, we conducted a pilot, open-label, single-site study of subjects who had pre-elected to undergo cryolipolysis on the inner thighs, back/bra fat, and/or submental areas. The objective of the study was to evaluate the safety and efficacy of FTB as an adjunct to NIBC, especially concerning post-procedure improvements in body skin firmness and texture.

MATERIALS AND METHODS

Study Design

This was an open-label, single-site, single-arm, 12-week pilot study to evaluate the safety and efficacy of FTB when applied twice daily for 12 weeks following cryolipolysis. Scheduled study visits occurred on days –28 to 1 (screening/enrollment), day 1 (baseline), day 14 (week 2), day 42 (week 6), and day 84 (week 12). Screening and enrollment could be part of the baseline visit. The study was conducted in accordance with guidelines for the protection of human subjects as outlined in 21 CFR 50, the accepted standards for Good Clinical Practice. The study protocol and all relevant addenda were reviewed and approved by Aspire IRB, Santee, CA. All subjects provided written informed consent prior to enrollment and study participation.

Study Population

Subjects 20 to 65 years of age, with Fitzpatrick skin types I–VI, who had pre-elected to receive cryolipolysis bilaterally on the inner thighs, back/bra fat, and/or submental regions were eligible to participate in the study. Inclusion requirements included general good health, absence of a disease state/condition that might impair study assessments or increase subject risk, and a willingness to maintain body weight within 5% of baseline weight. Potential subjects were excluded if they were pregnant, nursing, or planning to become pregnant; had any conditions that would make study participation unsafe or impair study assessments; had any contraindication to the body contouring device usage; had undergone invasive or noninvasive fat reduction procedures in the treatment area within the previous 6 months; or had excessive skin laxity in the treatment area(s).

Study Treatment

After study admission, subjects underwent their pre-elected cryolipolysis treatments on day 1 (baseline) after completing baseline pretreatment assessments. All subjects pre-elected, and were candidates for, CoolSculpting® or CoolSculpting® Elite (Zeltiq Aesthetics, Inc., an AbbVie Company, Pleasanton, CA). Subjects were offered the option to undergo an additional cryolipolysis treatment at week 2 or week 6. The investigator applied FTB to the cryolipolysis-treated area(s) during the same treatment visit using a prespecified number of US quarter dollar–sized amounts (quantity of product). Subjects subsequently applied FTB twice daily (morning and evening) commencing the day after the cryolipolysis treatment visit by smoothing the product onto the cryolipolysis-treated area until fully absorbed for 12 weeks. Adherence to the prescribed treatment was confirmed by assessing the amount used (by weight) at each study visit.

Assessments

Body skin texture and body skin firmness were graded separately by investigators on 10-point scales and assigned to categories: none (score of 0), mild (1–3), moderate (4–6), or severe (7–9). For body skin texture, scoring ranged from none (score of 0; no roughness or crepey texture of the treatment area; skin is completely smooth) to severe (7–9; marked roughness and/or crepey texture of the treatment area). For body skin firmness, scoring ranged from none (0; no sagging or droopy appearance of the treatment area; area appears completely smooth, firm, and taut) to severe (7–9; marked sagging and/or droopy, loose skin appearance of the treatment area). Whenever possible, each subject was graded by the same investigator throughout the study.

Each subject completed a self-assessment questionnaire comprising a series of statements about effectiveness immediately after FTB use (8 statements), effectiveness with continued FTB use throughout the study (15 statements), and product attributes (10 statements). Subjects evaluated each statement on a 4-level scale ("agree strongly" to "disagree strongly"). The questionnaire also included a single statement regarding overall satisfaction with treatment, ranging from "excellent" (very satisfied) to "poor" (not satisfied at all).

Two-dimensional (2D) imaging employed the Canfield IntelliStudio® and accompanying instructions (Canfield Site User Manual; Canfield Scientific, Parsippany, NJ) to capture and compare digital images of the treated areas before and after cryolipolysis and FTB treatment.

Investigator assessments and 2D imaging were conducted at baseline (day 1; prior to body contouring procedure[s]) and on days 14, 42, and 84. Self-assessment questionnaires were administered on days 14, 42, and 84. All assessments were completed within ±3 days of the target day.

The occurrence of FTB-related adverse events (AEs) and serious AEs (SAEs) was based on spontaneous subject reports (subjects were asked to report any adverse reactions or symptoms) or reports during study visits. Each AE/SAE report was reviewed by the investigator to assess AE severity, relationship to the study treatment (ie, unlikely/possible/probable), and resolution.

Statistical Methods

Because this was a pilot study, no formal sample size calculations were performed. All efficacy and safety analyses were conducted on the intent-to-treat (ITT) population, defined as subjects who completed the baseline visit and at least 1 follow-

up timepoint visit. For efficacy variables, baseline-to-timepoint comparisons were conducted using paired *t* tests on the ITT population. Statistical significance was set at $P<0.05$. Descriptive and summary statistics (eg, mean, standard deviation) were conducted on the ITT group. Percentage changes were calculated from numerical scores using the formula: (timepoint score – baseline score)/baseline value. Because score reductions indicate improvement, calculated percentage changes were multiplied by –1 for graphing purposes so that increases indicate improvement. For self-assessment questionnaires, responses of "strongly agree" or "agree" ("excellent", "good", or "fair" for the overall satisfaction question) were scored as positive. Safety analyses included tabulation of all AEs/SAEs in the ITT group and listing of incidence, severity, and relationship to study treatment for each event.

RESULTS

Study Population

A total of 17 subjects (16 female; 1 male) were enrolled and 14 subjects (82%) completed the study; reasons for discontinuation included work schedule conflict (n=2) and an AE (pruritus [n=1] of mild severity with a probable relationship with FTB treatment). Subject demographics, cryolipolysis technique, target area, and Fitzpatrick skin types are summarized in Table 1.

TABLE 1.

Baseline Subject Demographics and Procedures	
Characteristics	**All Subjects (N=17)**
Sex, n (%)	
Female	16 (94%)
Male	1 (6%)
Age range, y	25 to 63
Race/Ethnicity, n (%)	
Caucasian/White	7 (41%)
African American/Black	5 (29%)
Hispanic	4 (24%)
Asian	1 (6%)
Cryolipolysis procedure, n (%)	
CoolSculpting®	8 (47%)
CoolSculpting® Elite[a]	9 (53%)
Body area treated, n (%)	
Submental[a]	5 (29%)
Inner thighs	6 (35%)
Back/bra fat	6 (35%)
Fitzpatrick skin types, n (%)	
II	3 (18%)
III	7 (41%)
IV	3 (18%)
V	2 (12%)
VI	2 (12%)

[a]One subject elected to undergo an additional CoolSculpting® or CoolSculpting® Elite submental treatment at week 6.

Investigator Assessments

For both body skin firmness (Figure 1A) and body skin texture (Figure 1B), at week 2, statistically significant improvements versus baseline were observed in the inner thighs and the back/bra fat area ($P\leq0.02$), with numerical improvement versus baseline in firmness and texture in the submental region. Continued improvements in both firmness and texture across body areas were observed from week 2 onward, at week 6, and week 12. At week 12, mean improvements from baseline in firmness were 63% for upper and inner thighs and the posterior axillary area and 56% for the frontal neck/submental region; mean improvements versus baseline in texture were 59%, 71%, and 52%, respectively. Statistically significant changes from baseline for body skin firmness and body skin texture across all treated body areas indicated progressively improving body skin firmness and texture across all body sites ($P\leq0.0006$ vs baseline for all time points; Figure 1C).

Self-Assessment Questionnaires

Subjects strongly supported statements indicative of improved overall skin quality immediately following the use of FTB (Figure 2A). The strongest endorsements (>90%) were for "made my skin feel hydrated" and "made my skin feel smooth and soft." With continued use, more than 70% of subjects agreed that FTB improved skin firmness, smoothness, and overall appearance (Figure 2B). Additionally, subjects indicated that FTB was an effective adjunct to cryolipolysis, especially with regard to enhancement of overall aesthetic outcomes (71% agreed; Figure 3). More than 80% of subjects agreed that FTB was easy to apply, rapidly absorbed, and nongreasy, and had a pleasant texture and neutral smell (data not shown). Positive responses to the single overall satisfaction question were 88% at week 2, 92% at week 6, and 86% at week 12.

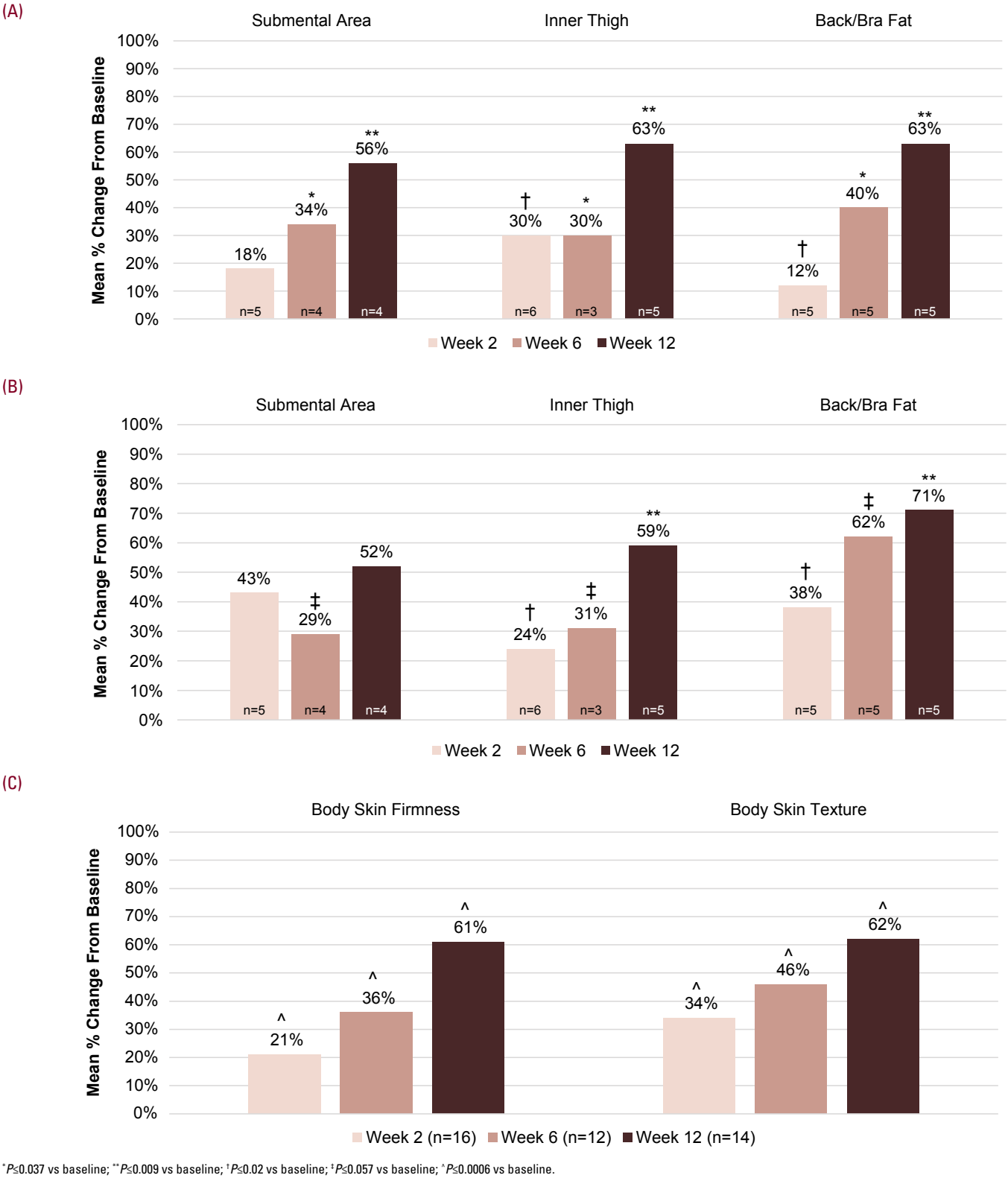
Photographic Evidence

Figure 4 shows representative examples of participant improvements in skin quality at week 12.

Safety

Two subjects reported 1 AE each during the study. Both AEs were mild in severity and considered probably related to FTB. One subject experienced pruritus on the inner thighs, resulting in discontinuation, and another subject experienced insomnia secondary to caffeine sensitivity that did not lead to discontinuation. Both AEs resolved without further sequelae.

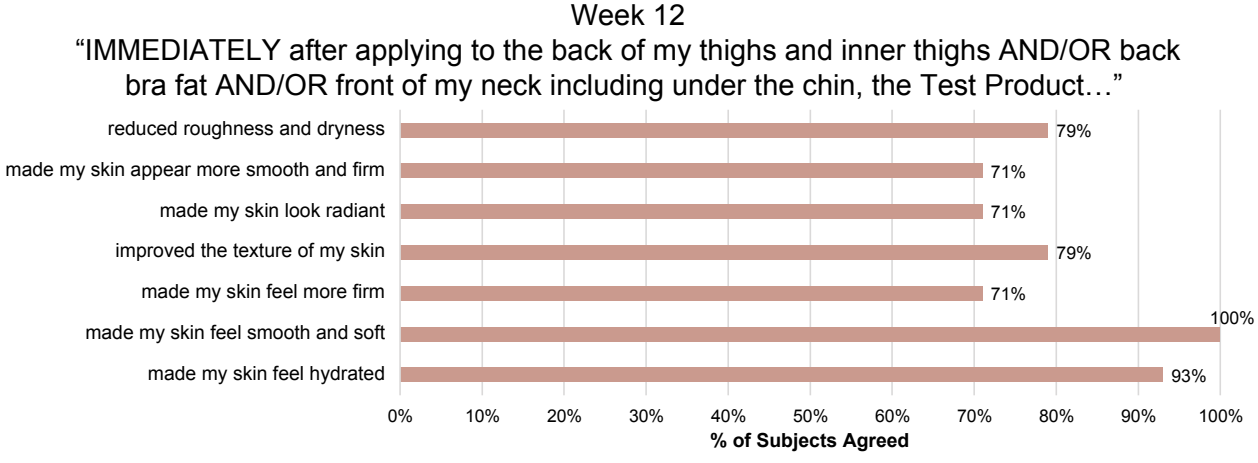
FIGURE 1. Improvement from baseline in mean scores (investigator assessment) for (A) body skin firmness and (B) body skin texture, according to the treated site, after 2, 6, and 12 weeks of treatment with firming and toning body lotion. (C) Pooled results for body skin firmness and body skin texture at all sites after weeks 2, 6, and 12.



*$P \leq 0.037$ vs baseline; **$P \leq 0.009$ vs baseline; †$P \leq 0.02$ vs baseline; ‡$P \leq 0.057$ vs baseline; ^$P \leq 0.0006$ vs baseline.

FIGURE 2. Self-assessment questionnaire statements with respect to overall skin improvement with which ≥70% of respondents agreed at week 12 (n=14), (A) immediately following firming and toning body lotion (FTB) application, and(B) with continued use of FTB.

(A)



(B)

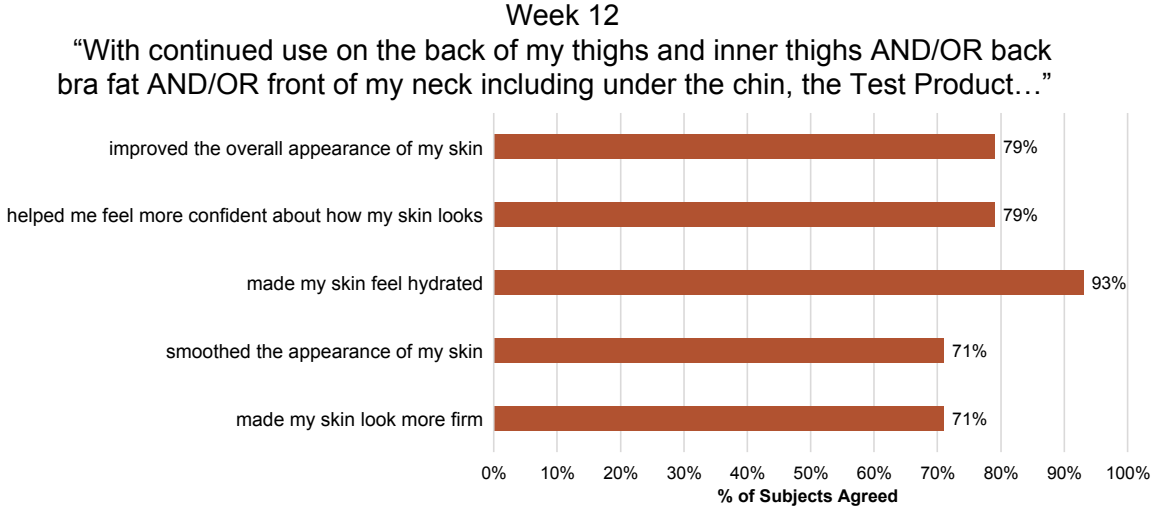


FIGURE 3. Self-assessment questionnaire statements with respect to continued use of firming and toning body lotion as an adjunct to pre-elected cryolipolysis treatment with which ≥70% of respondents agreed at week 12 (n=14).

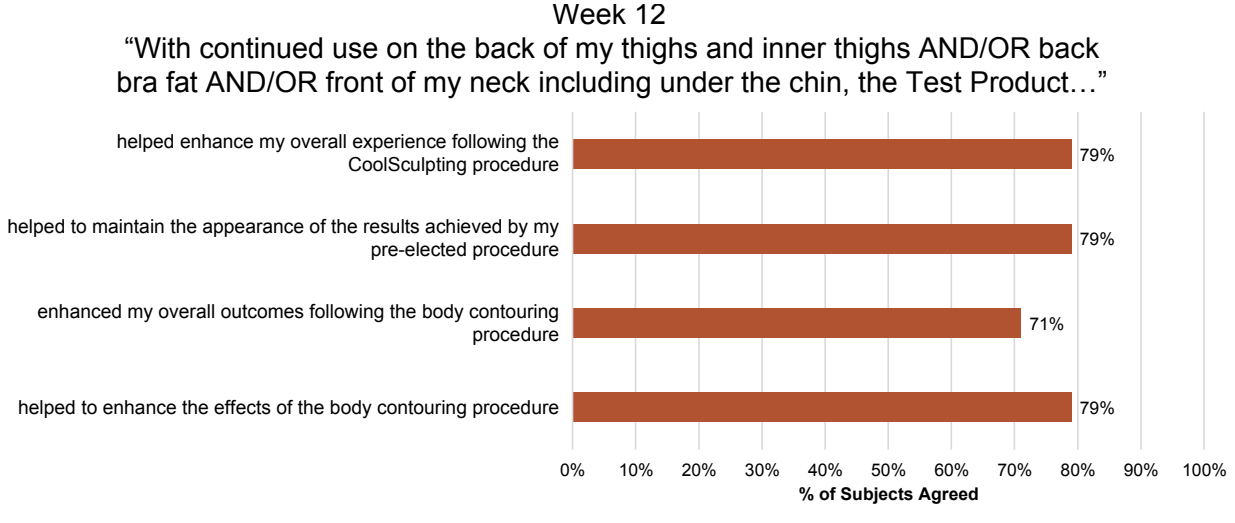
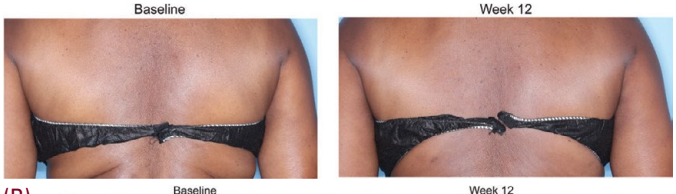
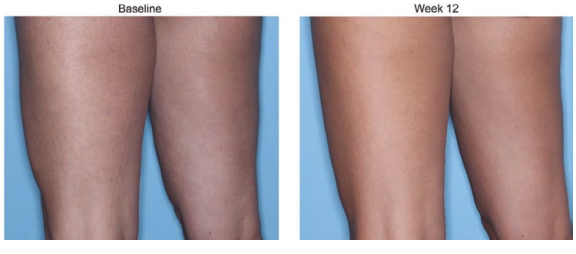


FIGURE 4. Representative photos of skin quality at baseline (left) and at week 12 (right). (A) 63-year-old African American female participant (Fitzpatrick skin type VI) who underwent cryolipolysis of the back/bra fat area followed by 12 weeks of twice-daily FTB application. (B) 41-year-old White female participant (Fitzpatrick skin type III) who underwent cryolipolysis of the inner thighs followed by 12 weeks of twice-daily FTB application. Note improvements in skin firmness, skin tone evenness, and visual skin texture.

(A)



(B)



DISCUSSION

This pilot study evaluated FTB as a topical skin treatment for patients undergoing cryolipolysis to further improve the appearance and aesthetic appeal of the overlying skin. Investigator assessments documented significant progressive improvement in cosmetic outcomes, including body skin firmness and skin texture at all treated sites, starting at the first assessment at week 2 and continuing through week 12. Investigator assessments were supported by photographic evidence and high rates of participant overall satisfaction with post-procedure efficacy of FTB, both immediately post-application and at week 12.

Many topical body skincare products are commercially available, but few of them are supported by clinical studies that assess their efficacy in improving skin quality.[20] FTB was shown to be tolerable and effective in improving body skin quality (including firmness, sagging, crepiness, skin smoothness, texture, skin tone evenness, and cellulite) when applied to the upper arms and thighs.[2] NIBC procedures, such as cryolipolysis, that lead to subcutaneous fat layer reduction through controlled cooling may also improve skin quality, including skin laxity in the back, buttocks, abdomen, flanks, and submental area.[18,21,22] One study evaluating the effectiveness of post-cryolipolysis use of a topical skin treatment designed to augment post-procedure debris removal with respect to skin laxity of the upper arms demonstrated a trend for improvement but lacked the support of statistical analysis.[23] In contrast, in the present study, FTB following cryolipolysis significantly improved firmness and laxity as early as week 2 (for inner thighs and back/bra fat) or week 4 (for submental region) compared with baseline (before cryolipolysis and FTB), which may be attributed to the multimodal approach of FTB targeting several key pathways in body skin health and rejuvenation in addition to cryolipolysis to optimize treatment outcome.[1]

The care of body skin as a distinct goal in aesthetic medicine has attracted rapidly expanding interest in recent years, driven in part by a desire to balance improvements in body skin care with those already achieved in the care of the aging face, and in part by the significant growth in NIBC procedures.[8,9] It has become clear that the rational development of topical products for body skin improvement holds the potential to augment and improve post-procedure patient outcomes.[1,20] This study evaluated the use of a topical adjunct to cryolipolysis in the back body fat and inner thigh regions, areas that are rarely addressed in clinical studies of skincare products on body skin.

In our work on the elucidation of pathways capable of supporting general skin health and rejuvenation, we identified pathways of potential value with respect to post-procedural recovery in body skin, including support for autophagy (recycling of fat droplets and other cellular debris), proteasome activation (recycling of damaged and misfolded proteins), lymphatic drainage, and lipolysis.[1,20,24] In vitro evaluation of the identified botanical components of FTB using a 3-dimensional human skin model has confirmed their ability to induce the expression of genes critical to each of these key pathways after 24 hours of incubation; similar results were observed using ex vivo human abdominal skin after 3 days of incubation.[1,2] Although the rapid induction of gene expression may help explain the early (immediate and day 3) clinical effects of FTB, additional work is required to firmly correlate changes in gene expression with these effects and with the continued improvements in skin quality over 12 weeks of treatment, as there are multiple steps, control points, and pathway interactions that lie between gene transcription and observable effects on skin.

Limitations of the current study include its small size, open-label design, and lack of a control group to facilitate direct comparison with cryolipolysis alone. In addition, as an initial study assessing the potential benefit of using FTB in combination with body contouring procedures, objective instrumentation-based analyses of hydration, firmness and elasticity, and skin density (eg, Corneometer, Cutometer, and optical coherence tomography, respectively) were not performed in support of investigator and subject assessments. Instrumentation-based analyses, however, were employed in a larger double-blind, randomized, controlled study of FTB as a standalone treatment that showed objective improvements in skin hydration, firmness, elasticity, and density.[2] Instrumentation-based analysis will be applied in future large, randomized, controlled studies to further define the effectiveness and tolerability of FTB as an adjunct to aesthetic procedures. Moreover, this preliminary study achieved

its purpose in showing the feasibility of using a rationally designed firming and toning body lotion targeting several key pathways that contribute to skin function, strength, and integrity to improve skin quality after NIBC. The study's small size may have constrained the ability to establish statistical significance at the site-specific level. The statistical strength and strong trends illustrated in Figure 1C, along with the small size of each site-specific group, suggest that the potential exceptions to these trends (eg, less-than-expected improvement in thigh skin firmness at week 6 and greater-than-expected improvement in the texture of frontal neck/submental region at week 2) may reflect larger-than-expected SDs and/or outlier results.

FTB following cryolipolysis demonstrated a progressive, statistically significant, and clinically meaningful improvement in the key skin quality parameters of firmness and laxity, which may be important to patients seeking comprehensive/holistic aesthetic outcomes. FTB following cryolipolysis was well tolerated and FTB was well regarded by treated subjects as an adjunct to cryolipolysis. These results support further testing in a large, prospective, randomized, controlled clinical study to determine the safety and efficacy of using FTB post-NIBC to improve body skin firmness and texture as well as potentially other body skin quality parameters, such as crepiness and skin tone evenness, that may be of concern to patients seeking comprehensive/holistic aesthetic outcomes.

DISCLOSURES

Craig Teller is a Speaker, Trainer, and Investigator for Allergan Aesthetics, an AbbVie Company. Harmony Saqr is a Clinical Research Coordinator for Bellaire Dermatology Associates. Elizabeth Makino, Priscilla Huang, and Rahul Mehta are full-time employees of AbbVie.

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Data Sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

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CASE REPORT

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Cutaneous Squamous Cell Carcinoma In Situ on a Fingernail Treated With HPV Vaccine

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INTRODUCTION

Squamous cell carcinoma (SCC) is one of the most common malignant neoplasms, and its incidence is increasing.[1] Some patients are considered poor candidates for surgery due to the location of the tumor, health conditions, or having numerous lesions simultaneously. Human papillomavirus (HPV) infection may be involved in the development of SCC in some patients.[2] Previous reports have shown a significant reduction of the rate of SCCs after administration of quadrivalent human papillomavirus vaccine in patients with a history of multiple SCCs.[3] Additionally, various cases of inoperable SCC were successfully treated with systemic and intralesional (IL) HPV vaccine on the leg and dorsal hand.[4-7] We report a case of a 74-year-old man with a recurrent SCC in situ on the left fourth finger successfully treated with intralesional and systemic administration of recombinant human papillomavirus 9-valent vaccine (Gardasil-9 Merck & Co Inc).

CASE

A 74-year-old man with a 10-year history of biopsy-proven SCC in situ of the left fourth dorsal finger and no known past medical history presented with a large erythematous scaly plaque on the left ring finger (Figure 1A). A shave biopsy was performed, showing SCC in situ (Figure 2A). The patient had Mohs micrographic surgery on the affected area 5 years previously with tumor recurrence. Subsequently, the patient was treated with topical tretinoin 0.1%, Imiquimod 5%, and 5-fluorouracil 5% compound cream three times weekly for ten weeks with no improvement. After the patient declined radiotherapy and additional surgery, the patient was offered treatment with Gardasil-9. He received an intramuscular (IM) vaccine injection at week 0, week 9, week 28, and one final booster on week 63. IL injections were administered at weeks 3, 7, and 23, and one final IL at the time of the booster shot (week 63). During the course of the administration of IM and IL the tumor was noted to drastically decrease in size, but still retained a small (less than 2mm) focus.

FIGURE 1. Clinical regression of SCC in situ after intralesional and systemic treatment with HPV recombinant vaccine. (A) scaly erythematous, coalescing painful plaques on the left fourth dorsal finger. (B) clinical resolution after 56 weeks of systemic and intralesional treatment of HPV vaccine.

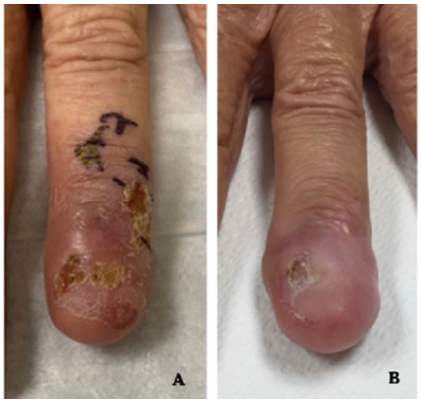
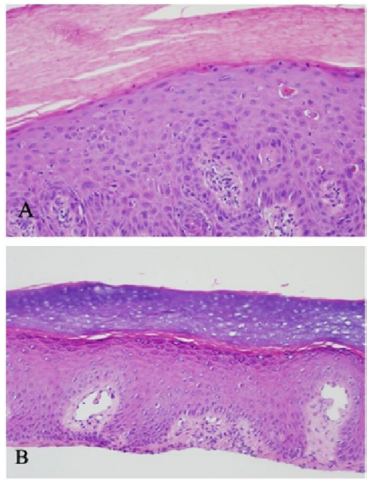


FIGURE 2. Histopathology before and after IM and IL treatment with HPV vaccine. (A) Initial biopsy showed dysplastic keratinocytes with marked nuclear atypia, multinucleation, and dyskeratosis, consistent with squamous cell carcinoma in situ. (B) two months after the final booster shot, a shave biopsy was performed, showing prominent granular layers with parakeratosis and no atypia, consistent with lichen simplex chronicus. (A and B), Hematoxylin-eosin stain: original magnifications (A, X400, B, X100).



At week 42, and before the final IL and IM booster shot, the patient was treated with topical chemotherapy, including a pea size amount of tretinoin 0.1%, 1/5 pk of Imiquimod 5%, and one drop of 5-fluorouracil 5% solution under occlusion, 3 times a week for 10 weeks. The topical chemotherapy was mixed and applied by the patient. No visible tumor was noted two months after the final booster injection (Figure 1B). A shave biopsy was performed, showing lichen simplex chronicus and no signs of atypia (Figure 2B). The patient tolerated the treatment well, and no additional treatment was needed. Full function of the finger and hand were maintained. He was followed up nine months after the last injection, and no visible tumor was present.

DISCUSSION

Surgical excision is the first-line treatment for SCC in situ. Radiotherapy, intralesional and topical treatments with multiple components may be considered as a primary treatment in patients that are not candidates for surgery.[8] However, not all patients are candidates for these treatments, and some SCCs are refractory to them. Gardasil vaccine is a recombinant, 9-valent vaccine commonly used as prophylaxis for certain types of cancer and has an excellent safety profile.

A patient with a 10-year history of recalcitrant SCC in situ on the left fourth dorsal finger was treated with IM administration of HPV vaccine with intralesional shots for 56 weeks with complete tumor resolution. To our knowledge, this is the first case of a SCC in situ treated in a finger. Of note, this patient received adjuvant topical treatment with topical tretinoin 0.1%, Imiquimod 5%, and 5-fluorouracil three times a week for 10 weeks. The patient received the combination treatment previously, with no improvement. We hypothesize that the vaccine worked synergistically with the tretinoin/fluorouracil/imiquimod combination. Other cases of successfully treated SCC with HPV vaccine are reported in the literature.[3-7] The first case report described the complete resolution of multiple basaloid SCCs on the right lower extremity of an elderly woman with a combination of systemic and intratumoral administration of the 9-valent HPV vaccine.[5]

Additionally, Nichols et al. reported two other patients with almost 65% overall reduction of new SCCs after a systemic quadrivalent HPV vaccine regimen(3). In another report, the combination of systemic and intratumoral 9-valent HPV vaccine resulted in the histologic cure of a large SCC in situ of the hand of a renal transplant recipient.[4-7] It is noted that the HPV vaccine has been shown to be a possible therapeutic strategy for actinic keratosis in immunocompetent patients, as reported in previous studies.[9]

This case adds to the growing body of evidence that the 9-valent HPV vaccine may be a well-tolerated and effective therapeutic option for patients with SCC or SCC in situ who are poor surgical candidates or who defer surgery. Additional studies are warranted to evaluate the efficacy and underlying mechanism of this treatment.

The authors would like to thank the patient who allowed us to present his case.

DISCLOSURES

Dr Correa-Selm is a consultant for Accutec Blades and a consultant and researcher for Novartis Pharmaceutical, also serves on the Advisory Board for the Jacinto Convit World Organization and the Dermatology Advisory Board for Melanoma Research Foundation. Dr Ioannides and Dr Badiavas have a patent pending for this application of human papillomavirus vaccine. No other disclosures are reported.

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CASE REPORT

Journal of Drugs in Dermatology

The Koebner Phenomenon in Bullous Pemphigoid

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INTRODUCTION

Bullous pemphigoid (BP) is a chronic, autoimmune subepidermal blistering disease typically presenting with widespread urticarial plaques, blisters, and pruritus. Localized variants of BP, such as peristomal, have been rarely reported in the literature.1–5 Herein, we report a case of peristomal BP that emerged after a colostomy. This case highlights the potential role of the Koebner phenomenon in the etiology and pathophysiology of peristomal BP.

CASE REPORT

A 70-year-old female with a history of dyshidrotic eczema, breast cancer, and diverticulitis presented to the dermatology clinic for a peristomal eruption that developed four months after a Hartmann procedure was performed for perforated diverticulitis. Examination of the abdomen revealed erythema, tense blisters, a rim of fine vesicles around the ostomy, and peristomal erosions (Figure 1). There were no other blisters present on cutaneous exam, other than palmoplantar, tense bullae, previously diagnosed as dyshidrotic eczema.

A punch biopsy was performed and demonstrated an intraepidermal vesicular mixed-cell infiltrate with eosinophils and gram-positive cocci, suggestive of acute allergic contact dermatitis with co-occurring staphylococcus aureus superinfection. The patient improved after a short course of oral antibiotics and topical steroids but subsequently flared.

FIGURE 1. Erythema, tense blisters on the central abdomen, a rim of fine vesicles around the ostomy, and peristomal erosions.

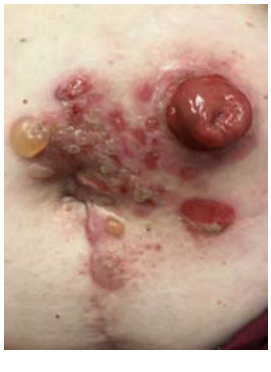


FIGURE 2. Dyshidrosiform BP with tense bullae on the palms.

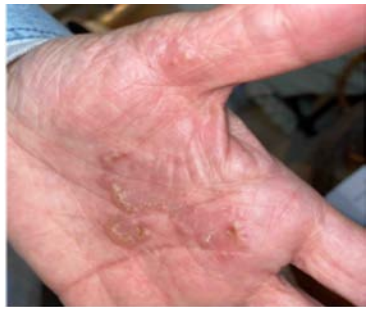
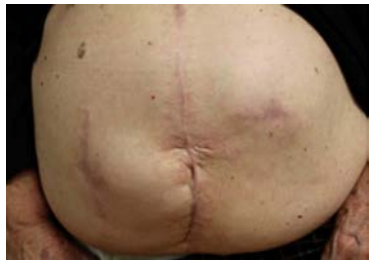


FIGURE 3. Resolution of peristomal BP with ostomy revision.



Repeat biopsy of the peristomal skin for histology and direct immunofluorescence was performed and showed subepidermal bullae with neutrophils and eosinophils and strong linear deposition of C3 along the dermal-epidermal junction. Serologies for bullous pemphigoid 180 and 230 antibodies returned at 36 and 107 enzyme-linked immunoassay units (upper limit of normal: 9), respectively, confirming the diagnosis of BP. The patient expressed a desire to avoid immunosuppressive medications and was started on doxycycline 100 mg twice daily, nicotinamide 500 mg twice daily, and desoximetasone 0.05% ointment twice daily. The abdominal eruption improved with treatment but did not resolve. The palmoplantar bullae also improved and were re-diagnosed as dyshidrosiform pemphigoid given the response to BP treatment (Figure 2).

Several months later, she underwent two surgeries to reverse the ostomy. Within two months of the ostomy revision, her abdominal eruption cleared and has not recurred (Figure 3).

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DISCUSSION

BP is a chronic, autoimmune subepidermal blistering disease that typically presents over the age of 65. Few cases of localized variants of BP, such as peristomal BP, have been previously reported, and like our case, the onset typically occurs within months of stoma placement.[1–5]

Patients with pre-existing BP may be at risk for developing peristomal BP.[6] The Koebner phenomenon describes new skin lesions appearing at sites of mechanical trauma in patients who carry a pre-existing dermatosis. Although the mechanism is unknown, it has been proposed that mucosal damage unmasks BP antigens in patients predisposed to BP or with pre-existing BP.[6] While reports of Koebner phenomenon in BP are rare, this mechanism may also explain trauma-induced BP, which has been reported secondary to surgical wounds.[7]

In this case, a diagnosis of peristomal BP was made in the absence of underlying medical conditions, highlighting the potential role of surgical trauma in the etiopathogenesis of this disorder. Her diagnosis of dyshidrotic eczema was subsequently revealed to be dyshidrosiform BP, which may have predisposed her to develop peristomal BP in the setting of trauma. In prior cases, the dyshidrosiform BP variant is often mistaken for dyshidrotic dermatitis.[8]

Current treatment guidelines take comorbidities and severity of BP into account. Traditional treatment options include topical and/or oral corticosteroids. Alternative therapies may include immunosuppressive drugs such as mycophenolate mofetil or azathioprine. For those with contraindications to immunosuppressive drugs, doxycycline or dapsone may be used.[9] In this case, we prescribed doxycycline 100 mg twice daily, nicotinamide 500 mg twice daily, and desoximetasone 0.05% ointment twice daily due to the patient's preference for non-immunosuppressive medications. Treatment improved the eruption, but ultimately, the reversal of the stoma resolved her symptoms. The resolution of the abdominal bullae with the removal of the potential nidus of inflammation coupled with ongoing dyshidrosiform BP points to the Koebner phenomenon as a potential driver of peristomal BP.

This case highlights the potential role of the Koebnerization phenomenon in the pathogenesis of peristomal BP. Dermatologists should consider a diagnosis of peristomal BP with the onset of bullae near a colostomy site, especially in a patient with pre-existing bullous disease. The literature on this topic is limited, and larger studies are needed to better understand the etiology and pathophysiology of peristomal BP.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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CASE REPORT

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Mitogen-Activated Protein Kinase Inhibitor-Induced Inflammatory Alopecia in Woman With Ovarian Cancer

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ABSTRACT

Inflammatory alopecia is an increasingly reported side effect of targeted cancer therapies. Here we report one case of inflammatory alopecia secondary to mitogen-activated protein kinase kinase (MEK) inhibitor agent Trametinib in a woman with ovarian cancer. Biopsies of the scalp were consistent with early scarring alopecia compatible with drug-induced alopecia. Significant improvement in hair loss occurred after treatment with intralesional Kenalog (ILK) injections and oral isotretinoin. Though acute alopecia has been described in patients using MEK inhibitors, this is the first reported case of inflammatory alopecia.

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INTRODUCTION

Targeted therapies against the mitogen-activated protein (MAP) kinase pathway, known to contribute to tumorigenesis, have emerged to treat a variety of cancers.[1] Mitogen-activated protein kinase kinase (MEK) inhibitors are FDA-approved for the management of melanoma, colorectal, and lung cancers that inhibit MEK1 and MEK2 activation.[1] In a clinical trial, MEK inhibitor, trametinib, use in patients with relapsed or persistent low-grade serous ovarian cancer yielded improved progression-free survival compared with standard-of-care therapies.[2] Trametinib is now used off-label to treat ovarian cancer with genetic alterations that increase MEK expression. Cutaneous adverse effects are the most frequent toxicity observed with MAP kinase pathway inhibitors. Adverse events are a common cause of targeted therapy dose interruption or reduction, thus highlighting dermatologic supportive care.[3,4] This is the first reported case of inflammatory alopecia following MEK inhibitor use.

CASE REPORT

A woman in her 50s with a history of bilateral ovarian cancer presented to an oncodermatology clinic with a new rash on her forehead and scalp. She started trametinib, a MEK inhibitor, five months prior for platinum-resistant recurrent disease with a *KRAS* G12D mutation. On examination, a diffuse acneiform rash was noted on her frontal scalp (Figure 1). Hair was sparse in the affected areas. She reported significant pruritus of lesions and frequent crusting. Diagnosis of acneiform eruption was favored; treatment with topical triamcinolone and oral doxycycline was started.

FIGURE 1. On presentation, mild scalp erythema with superimposed diffuse alopecia was noted with scattered papules and pustules.

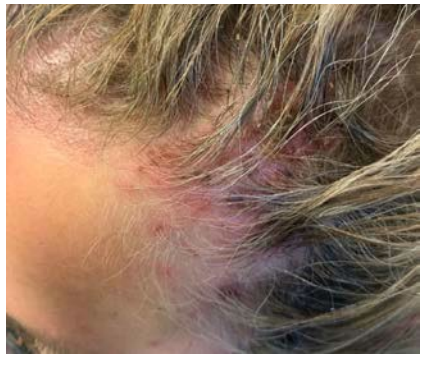

FIGURE 2. On follow-up, worsening alopecic patches were noted with background moderate erythema as well as overlying pustules and eroded papules. A biopsy was performed at this time.

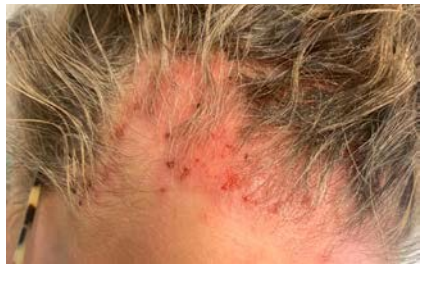

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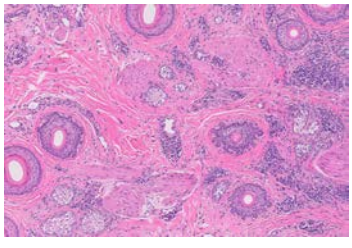
FIGURE 3. Hair in the telogen phase along with follicular miniaturization and extensive sebaceous gland atrophy. The background shows a perifollicular chronic infiltrate with increased plasma cells. H&E, 40x magnification.



Two months later, eruptions on her frontal scalp worsened (Figure 2) and she reported poor tolerance of doxycycline due to gastrointestinal side effects. Treatment was elevated to clobetasol 0.05% solution, clindamycin 1% lotion, and oral minocycline. A punch biopsy of the frontal scalp showed early scarring alopecia compatible with drug-induced alopecia, likely from Trametinib (Figure 3). Scalp lesion cultures grew clindamycin and tetracycline-resistant *Staph aureus*. Treatment with intralesional Kenalog (ILK), oral isotretinoin 20 mg, and a ten-day course of Bactrim was started. Significant improvement in lesions and hair regrowth was observed, so treatment was maintained.

While undergoing an unrelated surgery, she discontinued isotretinoin and reported a severe flare on her scalp. Improvement was seen after re-starting isotretinoin. Two months later, she reported significant crusting and pain on her scalp, and cultures again grew clindamycin and tetracycline-resistant *Staph aureus*, necessitating treatment with IV antibiotics. A dose reduction of trametinib was initiated and lesions fully resolved.

DISCUSSION

As MEK inhibitor use increases, their association with acute, non-scarring alopecia, perhaps a form of telogen effluvium, has been reported. A meta-analysis of the adverse effects of trametinib reported an alopecia prevalence of 13.3%,[4] mostly classified as Common Terminology Criteria for Adverse Events grade 1.[5]

When trametinib was used with BRAF inhibitor dabrafenib to treat melanoma, only 6% of patients experienced alopecia,[4] confirmed by another study when dabrafenib/trametinib were used together.[6] New hair kinking, a cutaneous adverse event secondary to BRAF inhibitors, was not observed in patients on combination BRAF inhibitor and MEK inhibitor therapy.[7] These studies suggest that trametinib's association with alopecia is blunted when combined with BRAF inhibitors.

Similar side-effect profiles are seen in MEK inhibitors and EGFR inhibitors including acneiform eruptions. A case of cicatricial alopecia was seen in a patient using EGFR inhibitor erlotinib, and as in our case, bacterial cultures of the scalp grew *Staph aureus*, suggesting that infection with *Staph aureus* superimposed with erlotinib therapy may lead to inflammatory alopecia.[7] Our patient's experience and others[8] support dermatologists should have a low threshold for scalp biopsy with bacterial cultures in patients with hair loss in areas of acneiform lesions when receiving MEK inhibitor therapy. As molecular targeted anti-cancer agents have shown benefit in cancers, dermatologists need to report and characterize less common reactions.

DISCLOSURES

The authors have no conflicts of interest to declare.

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CASE REPORT

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Oral Lichen Planus Successfully Treated With Upadacitinib

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ABSTRACT

With the rise of Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) inhibitor use in dermatologic conditions there has been increasing hope in treating extensive, and difficult to treat inflammatory cutaneous conditions. Today we report a case of oral lichen planus successfully treated with an oral JAK1 inhibitor, upadacitinib. This case had been unresponsive by several standard methods but responded with 70% improvement within 1 month when treated with upadacitinib.

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INTRODUCTION

Oral lichen planus (OLP) is an inflammatory mucosal disease, mediated by a predominantly T-cell lymphocytic response at the dermoepidermal junction.[1] With a global prevalence of approximately 1%, OLP can have a range of effects including significant chronic pain and sensitivity to the oral mucosa, and reduction in quality of life.[1] OLP classically presents bilaterally in the oral buccal mucosa as reticular white patches with or without ulcers.[1-2] The entire mechanism of OLP is not understood, but largely CD8+ cytotoxic and CD4+ Th1 T-cells and potentially Th9, Th17, and Tregs are thought to play a role in the T-cell mediated inflammatory response.[1] Factors including hepatitis C viral infection, drugs, and other variables can contribute to the development of OLP.[2] OLP can be challenging to treat, often managed by a variety of methods, predominantly treated with topical corticosteroids, topical calcineurin inhibitors, retinoids, and immunosuppressants.[2] Recently, the emergence of JAK inhibitor use in dermatology has been a helpful intervention in previously difficult to treat conditions.[3] Upadacitinib is a JAK-1 selective inhibitor used primarily in rheumatoid arthritis, that has shown promise in treating a variety of dermatologic diseases [3];however, it has only been cited twice in the literature to our knowledge as a treatment for OLP.[4-5] Our case documents a 70% improvement within 1 month of use of upadacitinib in a chronic, treatment-resistant case of OLP.

CASE

A 65-year-old female presented to the clinic with uncontrolled OLP. The patient has a history of OLP previously diagnosed by oral surgery via brush biopsy technique. Her medications include trazodone and triamterene-hydrochlorothiazide. Previously used medications and approaches included nystatin oral suspension, avoidance of metal utensils, triamcinolone 10 mg/cc intralesional injections, triamcinolone 0.1% dental paste and ointment, betamethasone cream, prednisone taper, and over-the-counter methods to alleviate her condition without success. The rash presented as white reticulated patches in the bilateral buccal mucosa. No ulcers were present. The rash was located on the bilateral vestibular mucosa, mandibular gingiva, palate, bilateral vestibular buccal cheek (Figure 1, Figure 2). No genital involvement was noted. Her condition was extensive, and her pain and irritation were severe, interfering with her ability to eat. She was treated with fluoride-free toothpaste, a topical mixture of viscous lidocaine, diphenhydramine, and Maalox Advanced 200-200-20 mg/5 mL oral suspension, and triamcinolone 5 mg/

FIGURE 1. Initial presentation of oral lichen planus on the right mucosal cheek.

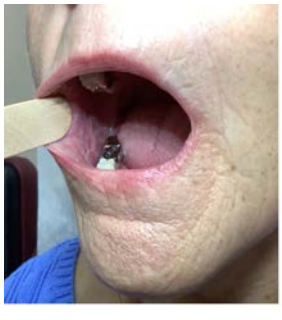

FIGURE 2. Initial presentation of oral lichen planus on the left mucosal cheek.

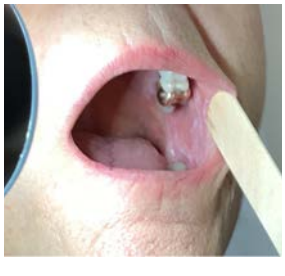

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FIGURE 3. Three-week follow-up of oral lichen planus on the right mucosal cheek.

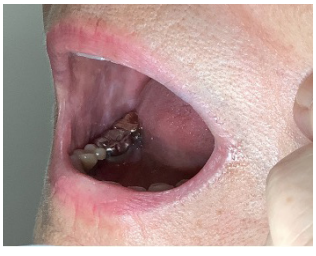


FIGURE 4. Three-week follow-up of oral lichen planus on the left mucosal cheek.

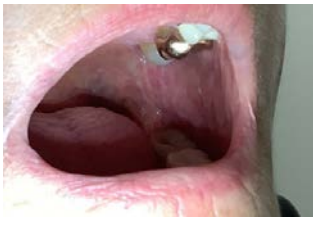
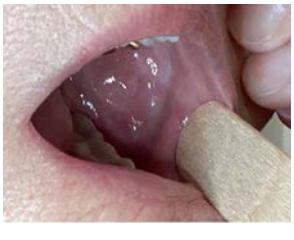


FIGURE 5. Improved oral lichen planus of the right mucosal cheek after one month of upadacitinib use.

FIGURE 6. Improved oral lichen planus of the left mucosal cheek after one month of upadacitinib use.



cc intralesional injections. The patient declined further topical corticosteroids due to previous side effects and lack of efficacy. Labs were ordered including: Quantiferon TB, Antinuclear Antibody panel, Hepatitis C Viral panel, and HIV 1 and 2 viral panels all of which were negative. Immunoglobulin E (IgE) was also drawn showing a mildly elevated value (538.0 IU/mL ref range: <114.0 IU/mL). At her 3 week follow up her improvement was unsatisfactory (Figure 3, Figure 4). There was consideration to start other immunomodulating agents such as mycophenolate, methotrexate, oral retinoids, and hydroxychloroquine, but the patient was not agreeable to their potential side effect profiles. In an attempt to achieve better control, the patient was started on upadacitinib 15 mg oral tablets once daily. At her one-month follow up she had significantly improved with a reported 70% decrease in irritation (Figure 5, Figure 6).

DISCUSSION

OLP is a painful, and sometimes ulcerative inflammatory cutaneous condition mediated by T lymphocytes.[1-2] Although the mechanism is not fully understood, OLP seems to largely rely on CD8+ and CD4+ Th1 lymphocytes, along with other T-cell subtypes.[1] There can be contributing factors in the development of OLP including hepatitis C in some cases,[2] which our patient screened negative for. OLP can be difficult to treat and sometimes can require the use of systemic therapy,[2] as it did in our case. Our patient presented with an elevated level of IgE, showing a value of 538.0 U/mL (ref range: <114.0 IU/mL), which in some cases can suggest a drug trigger.[6] Patch testing is still potentially planned to rule out an allergic etiology of her oral LP given a background of elevated IgE level Our patient had a chronic, long-standing clinical course of OLP with numerous treatments without success in controlling her condition. She was started on upadacitinib 15mg once daily with significant improvement achieved within 1 month of use. Upadactinib is a JAK-1 selective medication classically used in the treatment of rheumatoid arthritis.[3] JAK inhibitors have shown favorable outcomes in the treatment of challenging dermatologic diseases.[3] To our knowledge there have only been two documented cases of successful use of upadacitinib for oral lichen planus.[4-5] Baricitinib, a selective JAK1/2 inhibitor has been published once as a successful treatment for OLP[7]; and tofacitinib, a JAK1/3 inhibitor, is also published once in the literature as a case series involving 3 patients with successful treatment.[8] These cases collectively uncover a potential role in upadacitinib and other JAK inhibitors in the treatment of OLP.

CONCLUSION

Upadacitinib is a promising treatment option in difficult dermatologic conditions including OLP. In our case, the patient had chronic, extensive OLP with 70% improvement sustained within 1 month of upadacitinib use. More research on a larger scale following the efficacy of JAK inhibitors in dermatologic disease would be beneficial, but upadacitinib and other JAK inhibitors present an encouraging alternative for treatment-resistant cutaneous conditions including OLP.

DISCLOSURES

The authors whose names are listed above certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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BRIEF COMMUNICATION

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Dermatologists' Perspectives on Biosimilars

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ABSTRACT

Background: Biosimilars are biologic agents the Food and Drug Administration (FDA) has deemed to have no clinical difference from their reference biologics. In dermatology, biosimilars are approved for the treatment of psoriasis and hidradenitis suppurativa. Although dermatologists are high prescribers of biologics, they are more reluctant to prescribe biosimilars than other specialists. This survey-based study sought to characterize dermatologists' current perspectives on biosimilars.

Methods: A 27-question survey was distributed via email to dermatologists between September and October of 2022.

Results: Twenty percent of respondents would not prescribe a biosimilar for an FDA-approved indication. When asked about the greatest barriers to biosimilar adoption, 61% had concerns about biosimilar safety and efficacy, 24% reported uncertainty about state laws for interchangeability and substitutions, and 20% had concerns about biosimilar safety without concerns about efficacy. Thirty-five percent of respondents felt moderately or extremely knowledgeable about biosimilar interchangeability.

Conclusion: Biosimilars are safe and effective for treating approved dermatological conditions and may lower patient costs compared to their reference products. Patients are not always offered biosimilar therapy as an option, which may be due to unfamiliarity among dermatologists. This survey suggests a need for more research and educational initiatives, such as modules and workshops that focus on biosimilar safety, efficacy, and interchangeability guidelines.

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INTRODUCTION

Biologics are protein-based pharmaceuticals derived from living organisms that can treat autoimmune and inflammatory conditions.[1] Biosimilars are biologic agents the Food and Drug Administration (FDA) has deemed to have no clinical difference from their reference biologics.[2] Biosimilars are developed when the patent for the reference product expires.

The first biosimilar was approved by the FDA in 2015.[3] Currently, there are 39 biosimilars available, 11 of which are approved for psoriasis and hidradenitis suppurativa (HS), including biosimilars to adalimumab, etanercept, and infliximab.[4] Of these, only Cyltezo® (adalimumab-adbm) is considered interchangeable with its reference product, Humira® (adalimumab). Interchangeable biosimilars are FDA-approved to be substituted for their biologic at the pharmacy without input from the prescriber, although this is subject to state laws and regulations.[5] Although dermatologists are high prescribers of biologics, they are more reluctant to prescribe biosimilars than other specialists.[6,7] This survey-based study sought to characterize dermatologists' current perspectives on biosimilars.

MATERIALS AND METHODS

A 27-question survey was distributed via email to dermatologists who subscribe to the Dermatologist Magazine and those registered with IQVIA between September and October of 2022. Fifty-two dermatologists responded.

RESULTS

Survey Respondent Characteristics

Respondents' clinical practices focused on medical dermatology (71%), surgical dermatology (23%), pediatric dermatology (13%), cosmetic dermatology (13%), or a combination of all the above (27%). Most dermatologists worked in a single-specialty group practice with fewer than five offices (46%), followed by solo dermatology practice (31%) (Table 1). Sixty-four percent of practice revenue was derived from medical office visits and

TABLE 1.

Practice Setting (For this survey item, respondents were allowed to check all that apply)	
Answer Choices, % (n)	**Responses (n=52)***
Solo	31% (16)
Single-specialty group practice with fewer than 5 offices	46% (24)
Single-specialty group practice with more than 5 offices	8% (4)
Single-specialty group backed by private equity investment	2% (1)
Multispecialty group practice	8% (4)
Integrated health system	2% (1)
Hospital	4% (2)
Academic or research	4% (2)

*Respondents could select multiple practice settings, if applicable.

FIGURE 1. Patient characteristics who are most likely to be prescribed an interchangeable biosimilar.

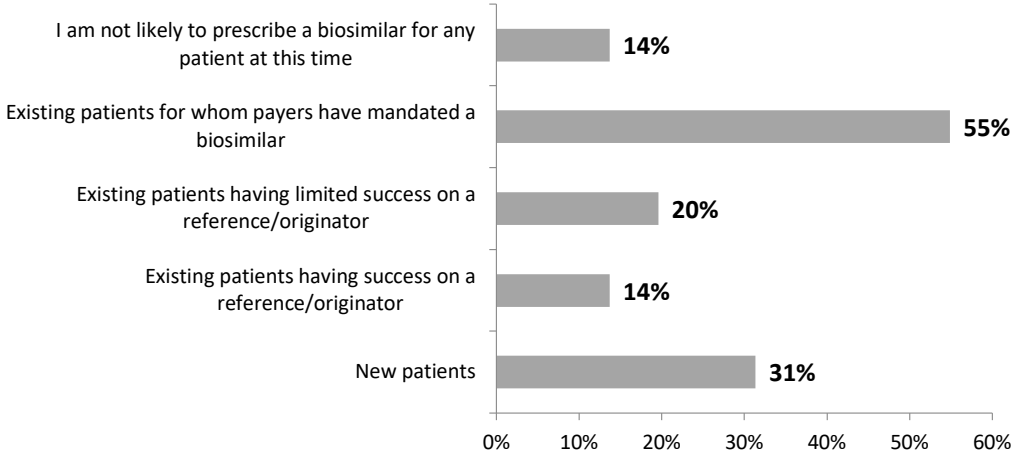

FIGURE 2. Understanding Biosimilar Interchangeability.

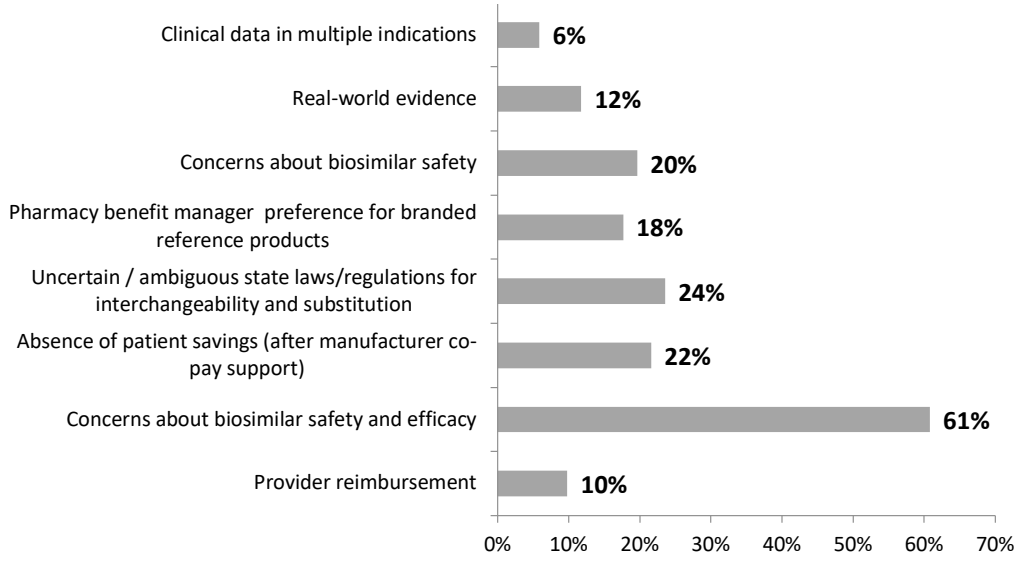

TABLE 2.

Understanding Biosimilar Interchangeability	
Answer Choices, % (n)	Responses (n=51)
Not at All Knowledgeable	10% (5)
Slightly Knowledgeable	20% (10)
Somewhat Knowledgeable	35% (18)
Moderately Knowledgeable	27% (14)
Extremely Knowledgeable	8% (4)

consults, followed by surgery (19%), non-surgical cosmetic procedures (8%), non-surgical medical procedures (7%), and office-dispensed dermatology product sales (2%).

Perspectives on Biosimilars

Twenty percent of respondents would not prescribe a biosimilar for an FDA-approved indication. Respondents were most likely to prescribe a biosimilar when it is mandated by payers (55%) and for new patients (31%). Fourteen percent of respondents were not likely to prescribe a biosimilar for any patient (Figure 1).

When asked about the greatest barriers to biosimilar adoption, 61% had concerns about biosimilar safety and efficacy, 24% reported uncertainty about state laws for interchangeability and substitutions, and 20% had concerns about biosimilar safety without concerns about efficacy (Figure 2). Thirty-five percent of respondents felt moderately or extremely knowledgeable about biosimilar interchangeability (Table 2).

Six percent of respondents were very unlikely to prescribe a biosimilar with an FDA interchangeability indication, while 16% were not likely, 22% were neutral, 47% were likely, and 10% were very likely. Eighteen percent of respondents were very unlikely to prescribe a non-interchangeable biosimilar, 38% were not likely, 30% were neutral, 12% were likely, and 2% were very likely.

DISCUSSION

Survey Respondent Characteristics

Most respondents' clinical practices focused on medical dermatology in a single-specialty group practice, where medical visits and consults comprised most of the revenue.

Factors That Discourage Biosimilar Adoption

There is hesitancy by dermatologists to prescribe biosimilars for indications that have been granted FDA approval, with a fifth of respondents stating they would not prescribe biosimilars. The average time to FDA approval for biologics is 12 years, and eight for biosimilars, and both share a similar approval process.[8] Dermatologists express a greater concern for the abbreviated FDA approval for biosimilars than other specialists, believing it impacts safety.[7] Concerns may also stem from the recent introduction of biosimilars for skin disorders.[3] Long-term safety and efficacy information for biosimilars is limited. Studies for psoriasis are limited to 52- and 55-week periods, while studies for HS are limited to international studies with small sample sizes.[9-13]

Knowledge of biosimilar interchangeability and the state laws that govern biosimilar substitution is also a barrier to biosimilar adoption. Only a third of respondents endorsed feeling moderately or extremely knowledgeable about biosimilar interchangeability. Although interchangeable biosimilars have comparable efficacy to their reference product and meet additional requirements for FDA approval compared to other biosimilars, only about half of respondents were likely or very likely to prescribe a biosimilar with an FDA interchangeability indication.[2] Uncertainty of state laws for interchangeability and substitution limit biosimilar adoption by placing the burden of understanding prescribing and substitution guidelines on the dermatologist and the pharmacist filling the prescription.[14]

Factors That Encourage Biosimilar Adoption

Our survey also identified organizational and patient factors that increased dermatologists' willingness to prescribe a biosimilar. Organizational factors include payor mandates. This may benefit patients as biosimilars cost up to 30% less than their reference biologic, which can exceed $10,000 for a single dose.[15] Respondents were also more willing to prescribe a biosimilar for new patients. Dermatologists may believe biosimilars are more effective in new patients who are treatment naïve. Alternatively, this may be evidence of dermatologists' hesitancy to switch established patients from a biologic to a biosimilar. However, nonmedical switches from a biologic to a biosimilar for psoriasis are supported by the biosimilar working group of the International Psoriasis Council.[16] In addition, nonmedical switches in psoriasis and HS do not impact clinical responses to therapy.[11,17]

CONCLUSION

Biosimilars are safe and effective for treating approved dermatological conditions and may lower patient costs compared to their reference products. Patients are not always offered biosimilar therapy as an option, which may be due to unfamiliarity among dermatologists. This survey suggests a need for more research and educational initiatives, such

as modules and workshops, that focus on biosimilar safety, efficacy, and interchangeability guidelines.

This survey was limited by a relatively small sample of respondents. Despite this, clear patterns emerged regarding provider factors limiting the adoption of biosimilars to treat dermatological conditions. Additionally, this survey explored a limited number of barriers and facilitators to the uptake of biosimilars by dermatologists.[18] Another potential limitation was the exclusion of dermatology residents and fellows, who may hold a different opinion of biosimilars than established, practicing dermatologists included in the survey.

Overall, the development of new biosimilars is ongoing due to market demand for cost-effective treatments. Although biosimilars in dermatology are currently limited to psoriasis and HS, the recent approval of biologics for other dermatologic conditions, such as pemphigus vulgaris and atopic dermatitis, foreshadows the development of biosimilars for these reference products. Biosimilars in dermatology are here to stay, with more in development, and there may be a need to educate dermatologists about their applications in clinical practice.

DISCLOSURES

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Topical Human Mesenchymal Stem Cell-Derived Exosomes for Acceleration of Wound Healing Following Tissue Trauma and Aesthetic Procedures: A Case Series

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ABSTRACT

Background: In the Aesthetics Practice, measures to accelerate wound healing and minimize downtime following procedures have been largely restricted to topical serums and platelet-rich plasma (PRP), which can have varying levels of success. Here, the authors present a case series of patients treated in clinical practice with cell-free exosomes derived from human placental mesenchymal stem cells (Exovex™, Exocelbio, Doylestown, PA). Topical administration of exosomes after either aesthetic treatment or traumatic injury (a dog bite) had a marked effect on healing. Effects were assessed visually and case-study images are shared. Individuals demonstrated significantly accelerated recovery and wound healing within hours to days, depending on the procedure. Patients who had undergone the same aesthetic procedure prior without exosomes reported satisfaction with reductions in pain, swelling, redness, and post-procedure downtime. No adverse events were reported by patients after treatment. Together, these case series suggest that exosome treatment can accelerate wound healing safely and effectively and support topical use in an office-based setting. These findings also highlight the need for more formal evaluation of the effects of exosomes on wound healing in reducing aesthetic procedure recovery times for surgical and non-surgical interventions.

Significant Finding: The case series presented here illustrates the potential for exosomes to be a versatile and important part of clinical care, especially in situations where expedited healing is central to patient safety and/or satisfaction. These results provide strong support for additional research.

Meaning: Topical administration of cell-free exosomes has the potential to improve patient care and satisfaction with aesthetic interventions. Early experience, illustrated by the presented case studies has been remarkably positive and treatment has the potential to dramatically improve the standard of care.

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INTRODUCTION

While surgical and non-surgical aesthetic technologies continue to evolve, there remains an unmet need for effective wound healing therapy in clinical practice. Although PRP has been widely and safely used in the clinic,[1,2] there are multiple limitations to its use as a wound healing therapy, including its extensive collection and preparation process and potential for decreased effectiveness in more mature patients.[3-5]

Exosomes, also known as extracellular vesicles (EVs), are lipid bilayer membrane micro-vesicles secreted by almost all eukaryotic cells.[6-8] Native exosomes target and repair damaged tissue at sites of inflammation through the delivery of lipids, proteins, and nucleic acids to recipient cells via paracrine signaling.[7,8] Their contents may also include cell-signaling proteins and/or growth factors relevant to all four phases of wound healing. The safe use of exosomes derived from a variety of cell types has been extensively reported for numerous therapeutic applications and their anti-inflammatory and immunomodulatory properties are well documented.[7,9]

The ability of exosomes to influence angiogenesis and the differentiation, proliferation, and apoptosis of target cells has made these micro-vesicles the subject of particular interest in wound healing and regenerative medicine.[10] In addition, many studies have demonstrated a role for certain miRNAs in the promotion of scar removal, skin rejuvenation, pigmentation regulation, and hair growth.[10]

MATERIALS AND METHODS

Exosome Source and miRNA Content

Cell-free exosomes were pre-clinically isolated from mesenchymal stem cells derived from human placental tissue according to good manufacturing practice (GMP) guidelines.[7]

Routine quality control (QC) testing (ie, nitriloacetic acid [NTA], next-generation sequencing [NGS], and multidimensional identification technology [MudPIT]) was performed to determine the quantity, size, miRNA contents, and purity of the exosomes.

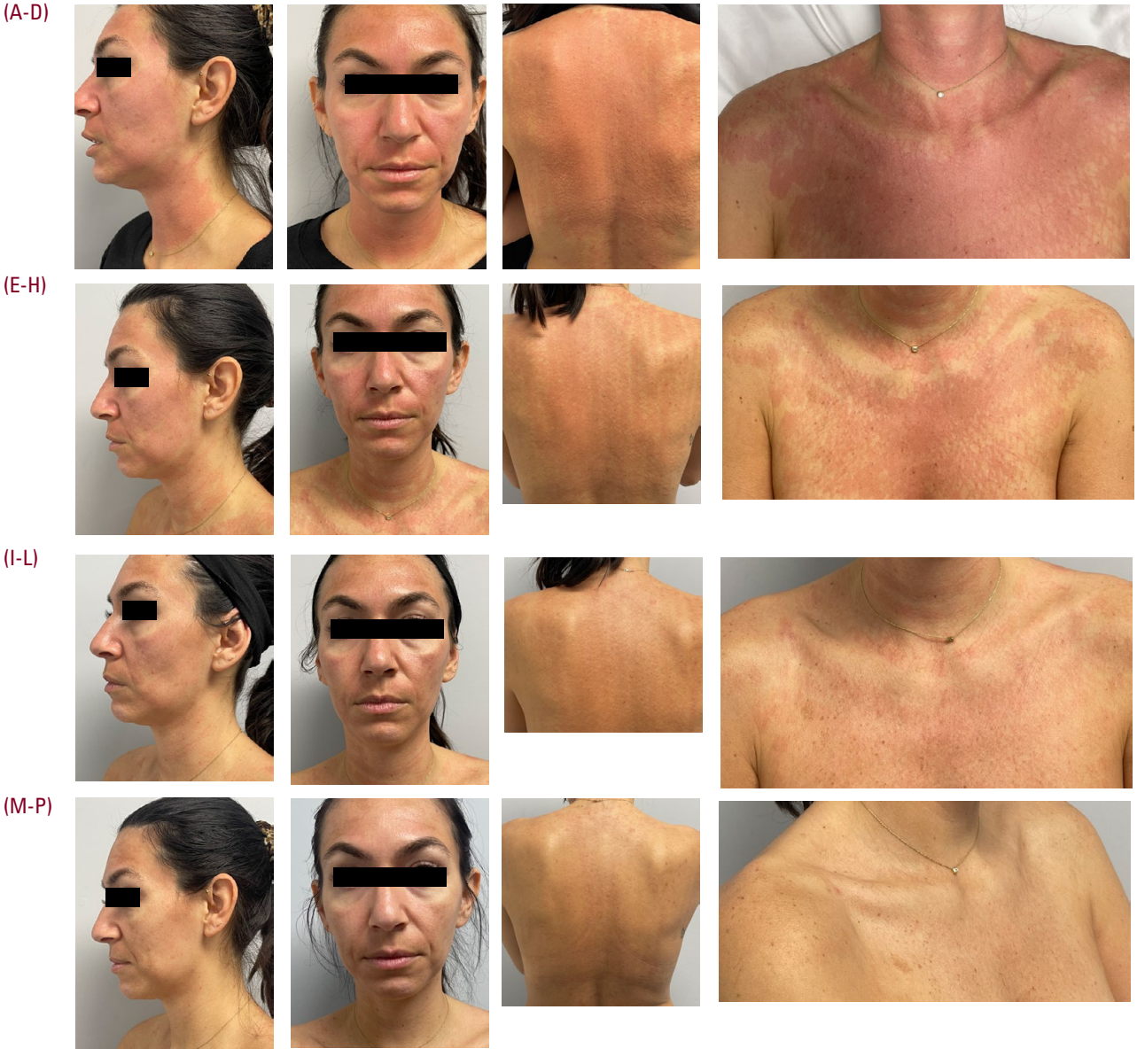
Intervention/Preparation of Intervention

Exosomes (Exovex™, Exocelbio, Doylestown, PA) are a cell-free preparation in pre-diluted vials of serum at 1 of 4 ready-to-use concentrations: 5 x 10^9 exosomes in 2 mL of serum, 12 x 10^9 exosomes in 2.5 mL of serum, 25 x 10^9 exosomes in 5 mL of serum, and 100 x 10^9exosomes in 5 mL of serum. Vials are stored at -20 °C until use and must be thawed without shaking before application. In each of the cases detailed below, exosome serum was applied topically. All patients presented here were treated in accordance with the principles outlined in the Declaration of Helsinki, and each patient consented to treatment and photography.

RESULTS

Case Study Patient 1: A 31-year-old woman with acne, mild acne scarring, and melasma who received fractional non-ablative laser treatment (Novel 1,927 nm Fractional Thulium Laser, LaseMD Ultra by Lutronic). The patient received

FIGURE 1. A 31-year-old female immediately after treatment with fractional non-ablative laser therapy for melasma (A-D) and 1 hour (E-H), 4 hours (I-L), and 24 hours (M-P) after topical exosome application.

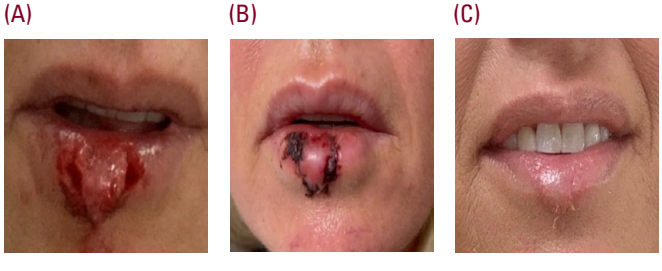


treatment at a moderate-to-high laser temperature (7 Joules) set for hyperpigmentation/melasma treatment (ie, random laser application to prevent overheating of the skin) to the face, chest, and back with 6 passes per treatment area.

After the last pass, the patient was assessed for discomfort and reported a pain level of 8 out of 10 for heat discomfort, stinging, and burning. After the assessment, a total of 3 mL of the 5 x 10^9 concentration of exosome serum was applied across the treatment areas. Immediately after application, the patient reported a reduction in severity of discomfort to a pain level of 4 out of 10. As observed in Figure 1, erythema and swelling recovery time was also reduced.

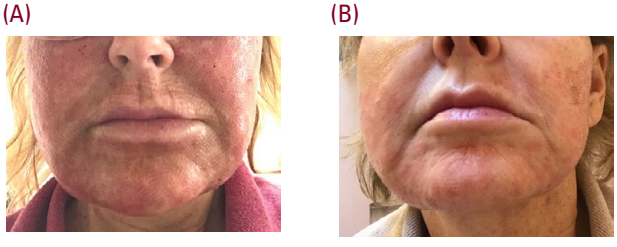
Case Study Patient 2: One drawback of PRP is that the bioactivity of platelets and growth factors isolated from older individuals may be less efficient than in younger counterparts, impacting the clinical effectiveness.[5] Therefore, comparing the efficacy of PRP vs exosome therapy in older patients is of particular clinical interest. In Figure 2, a 72-year old female patient is shown following after treatment with CO2 fractional laser therapy followed by PRP. The patient demonstrated erythema and swelling with PRP that continued for a week after treatment (Figure 2A). After receiving the same treatment, 4 years later, followed by 2.5 mL of the 12.5 x 10^9 exosome serum solution, the patient's skin showed reduced swelling at 4 days after treatment with minimal erythema and an overall reduction in peak post-treatment severity (Figure 2B). The reduced downtime, swelling, and discomfort contributed to increased patient satisfaction with the procedure.

FIGURE 3. A 49-year-old female immediately following a dog bite (A) and at 20 hours (B) and day 10 (C) after topical exosome application. Wound closure is aesthetically pleasing with minimal scarring.



Case Study Patient 3: A 49-year-old female patient who suffered a dog bite in the lower lip (Figure 3A) was treated by an emergency room physician (non-plastic surgeon) and presented for treatment 20 hours after wound stitching (Figure 3B). At this time point, the wound was cleaned with a hypochlorous acid solution, and 2.5 mL total of the 12.5 x 10^9 exosome solution was slowly applied, a few drops at a time, over 10 minutes using a 32 G ½" needle, allowing each aliquot of serum to be absorbed by the skin before the subsequent application. Wound

FIGURE 2. A 72-year-old female 4 days after treatment with CO_2 fractional laser followed by topical PRP (A) or topical exosomes (B). The photograph in panel B was taken four years after the image in panel A.



healing could be observed as early as 18 hours after exosome application. Although the emergency room estimate for healing of this type and location of traumatic injury was estimated to be 6 months, by day 10 (Figure 3C), the wound was completely closed, with no evidence of fibrotic tissue, and with minimal scarring and well preserved sensory and motor function. Within this time period, lip function was entirely restored, and evidence of scaring is nearly absent.

CONCLUSIONS

PRP is an autologous concentrate derived from a patient's own serum and its acquisition is a multi-step process that requires access to specific equipment and carries handling and contamination risks.[3] Furthermore, PRP can contain variable numbers of platelets and growth factors, which can affect bioactivity.[5] For more mature patients, PRP may not be able to provide enough of the cellular factors necessary, which is problematic as these are the patients who need healing and accelerated recovery the most. In contrast, harvesting and preparation of exosomes in a laboratory and according to GMP guidelines controls for variability in efficacy and removes the need for further manipulation in the clinic, allowing their application with no interruption in workflow and the expectation of a predictable level of bioactivity across patient populations and between batches.

The discovery of the ability of exosomes to act as carriers of genetic messages between cells has caused an explosion of interest in these micro-vesicles.[7] In 2020, exosomes carrying some of the same genetic material contained within the exosomes used in these case studies (miRNA 425-5p and 142-3p; Exovex™) were demonstrated to promote wound healing and to reduce scarring, potentially through the inhibition of transforming growth factor (TGF)-β1expression within injured tissue, suggesting a potential mechanism for their effects in promoting accelerated recovery time and traumatic injury.[11] Indeed, a clinical study investigating the safety and efficacy of human placental mesenchymal stem cell-derived exosomes in the acceleration of wound healing after infection was recently (June 2022) initiated, further evidence of the interest in their clinical potential.[12]

In these case studies, exosomes rapidly and dramatically accelerated recovery times for a range of patients with no reported adverse effects. For those patients who prioritize or require minimized downtime, exosomes are a valuable complement to treatment. For patients with the potential for scarring, this type of therapy may be invaluable, in particular for post-surgical scarring. That the patient in Figure 3 demonstrated dramatically accelerated wound healing (10 days to complete wound closure vs 6 months predicted) displayed no scarring or fibrosis is a testament to the potential therapeutic application of these vessels that is further backed by in vitro findings and recognition that exosomes can promote healing through various pathways at multiple stages in wound healing.[11,13] Taken together these case studies emphasize the need for further clinical study of these potentially significant modifiers of infection, inflammation, and wound healing following both trauma and surgical procedures.

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DISCLOSURES

Dr Peredo is a trainer for Galderma and an Advisory Board Member for Exocel Bio. Dr Shivananjappa is a Scientific Advisor for Exocel Bio.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Molecular Insights Into the Effects Of PLLA-SCA on Gene Expression and Collagen Synthesis in Human 3D Skin Models Containing Macrophages

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ABSTRACT

Injectable poly-L-lactic acid (PLLA-SCA) is used for the correction of shallow to deep nasolabial fold contour deficiencies, cheek wrinkles, and other facial wrinkles. In contrast to hyaluronan (HA) fillers, PLLA-SCA has a biostimulatory effect by activating resident fibroblasts to produce collagen, but the mechanisms are not known in detail at the molecular level. Therefore, our aim was to investigate the molecular effects of PLLA-SCA in a comprehensive in vitro study. Since PLLA-SCA-dependent collagen production in fibroblasts depends on the interaction with macrophages, we generated novel macrophage-containing 3D skin models. According to the clinical application, PLLA-SCA was injected once into the dermal equivalent of the 3D skin model. Histological analysis showed a significant increase in epidermal thickness in these models after 5 and 14 days. Gene expression profiling revealed an upregulation of integrins and laminins (e.g., LAMA3, ITGA6), which are essential components of the dermal-epidermal junction. In addition, we found an upregulation of cytokines and chemokines (TGFB2, CXCL6, IL1B) at day 14 after PLLA-SCA injection. Interestingly, immunohistochemical analyses exhibited a significantly stimulated collagen I production in our models. These effects might be attributed, at least in part, to the upregulation of IL1B and subsequently CXCL6, which stimulates collagen I synthesis in human dermal fibroblasts as we could demonstrate. Taken together, our data provide for the first time molecular insights into the biostimulatory effects of PLLA-SCA on collagen I production in novel human 3D skin models comprising macrophages.

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INTRODUCTION

Poly-l-lactic acid (PLLA-SCA) is a synthetic polymer used as an injectable to restore volume and stimulate collagen formation.[1] It was initially approved by the US Food and Drug Administration (FDA) in 2004 under the name Sculptra® (Galderma) for the treatment of HIV-associated lipoatrophy.[2] Later in 2009 it was approved as Sculptra® Aesthetic for the correction of shallow to deep nasolabial folds and other facial wrinkles in immunocompetent patients.[3] In 2023, the FDA has approved Sculptra® for the correction of cheek wrinkles.[4] PLLA-SCA has a biostimulatory effect by activating resident fibroblasts to produce collagen.[3,5] Animal experiments revealed that after injection, PLLA-SCA induces a response through phagocytosis by tissue macrophages and then slowly converts into lactic acid monomers, which are metabolized into carbon dioxide or incorporated into glucose while stimulating the production of new collagen type-I fibers in the skin.[1,6] However, the underlying molecular mechanisms are not yet known in detail. Since our previous study aimed to better understand the molecular effects of HA-based fillers with and without subsequent additional fractional laser co-treatment,[7] we now focused on gaining molecular insights into the stimulatory effects of PLLA-SCA injections on collagen I production in novel human 3D skin models comprising macrophages.

MATERIALS AND METHODS

In this in vitro study, the PLLA-SCA filler Sculptra® was injected into previously described human full-thickness 3D skin models,[8] in which macrophages were incorporated. Macrophages were isolated from peripheral blood mononuclear cells (PBMCs) by plastic adherence as published before[9] and added to the models on day 2 of culture. Sculptra® is composed of 150 mg of PLLA-SCA microparticles with a median particle size of approximately 50 µm suspended in sodium carboxymethylcellulose (NaCMC).[10] After one single injection of 100 µl Sculptra®, models were harvested after 5 and 14 days for histological and gene expression analyses. Untreated models were used as negative controls. Experiments were performed three times independently with three different cell donors.

Microarray analysis was performed as previously described[11] by using Clariom™ S assays (Thermo Fisher Scientific). Immunofluorescence staining was done using an anti-collagen I antibody (ab34710; Abcam, Waltham, MA).

For monolayer experiments, primary dermal fibroblasts were stimulated with human recombinant CXCL6 (50 ng/ml) for 24 hours.

Statistical analysis was performed using the Mann-Whitney U test. Values of $P<0.05$ were considered statistically significant.

RESULTS

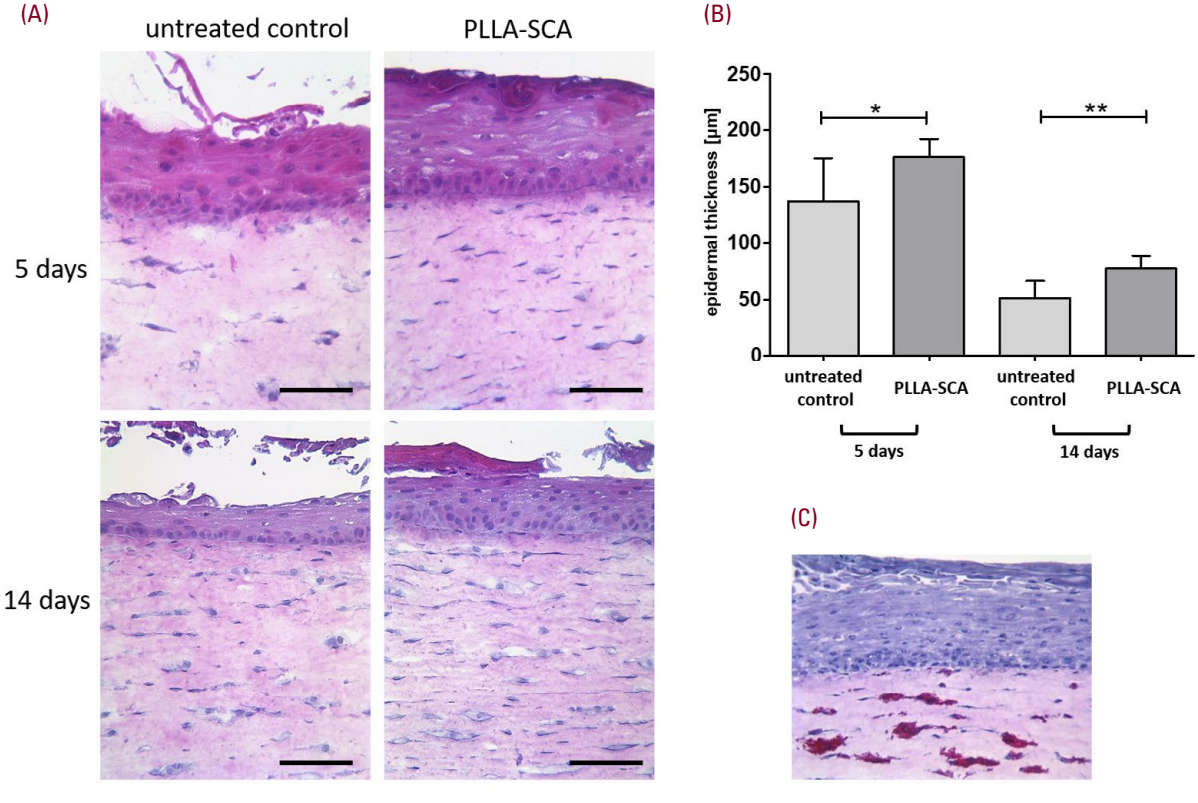
Histological analysis revealed a significantly increased epidermal thickness in our macrophage-containing 3D skin models at days 5 and 14 after PLLA-SCA injection compared to untreated controls (Figure 1A and B). Using immunohistochemical staining, we could prove that our models contained CD163-positive macrophages (Figure 1C).

On the molecular level, microarray analyses showed an upregulation of integrins (ITGA6), laminins (LAMA3, LAMC2), and desmogleins (DSG2) at day 14 after PLLA-SCA injection into the models, compared to untreated controls (Figure 2). Furthermore, we found an upregulation of cytokines (TGFB2, IL1B) and chemokines (CXCL6).

Focusing on the biostimulatory effects of PLLA-SCA on collagen production, we performed an immunofluorescence analysis of collagen I expression (Figure 3A). Quantitative fluorescence measurements revealed a significant upregulation of collagen I at day 14 after PLLA-SCA injection (Figure 3B).

To test whether CXCL6, which was upregulated in our microarray analysis, could be a potential stimulator of collagen I in the human skin, we stimulated primary dermal fibroblast monolayers with a human recombinant CXCL6 protein. An ELISA assay revealed an upregulation of collagen I in dermal fibroblasts after CXCL6 stimulation for 24 hours (Figure 3C).

FIGURE 1. (A) Representative HE stained sections of 3D skin models on day 5 and day 14 after intradermal injection of a poly-l-lactic acid (PLLA-SCA)-based filler. (B) Measurement of epidermal equivalent thickness on days 5 and 14 after PLLA-SCA injection. (C) Representative immunohistochemistry staining of CD163-positive macrophages within the 3D skin models.



Data are given as arithmetical means ± standard deviation; *$P<0.05$, **$P<0.01$.

FIGURE 2. Representative microarray analysis shows regulation of different genes in a 3D skin model, on day 14 after PLLA-SCA injection, compared to untreated control.

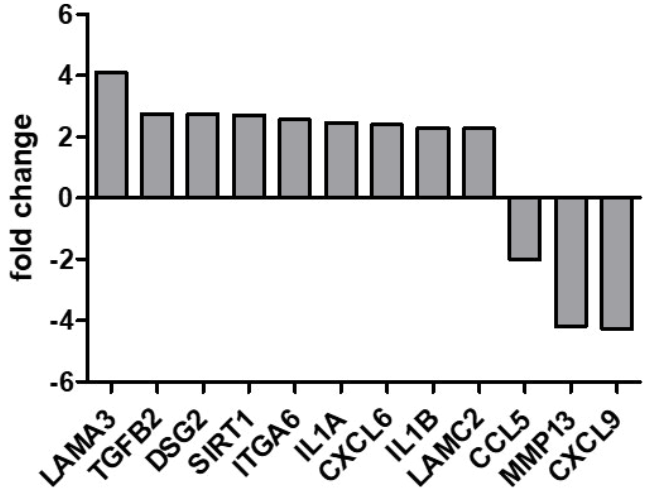
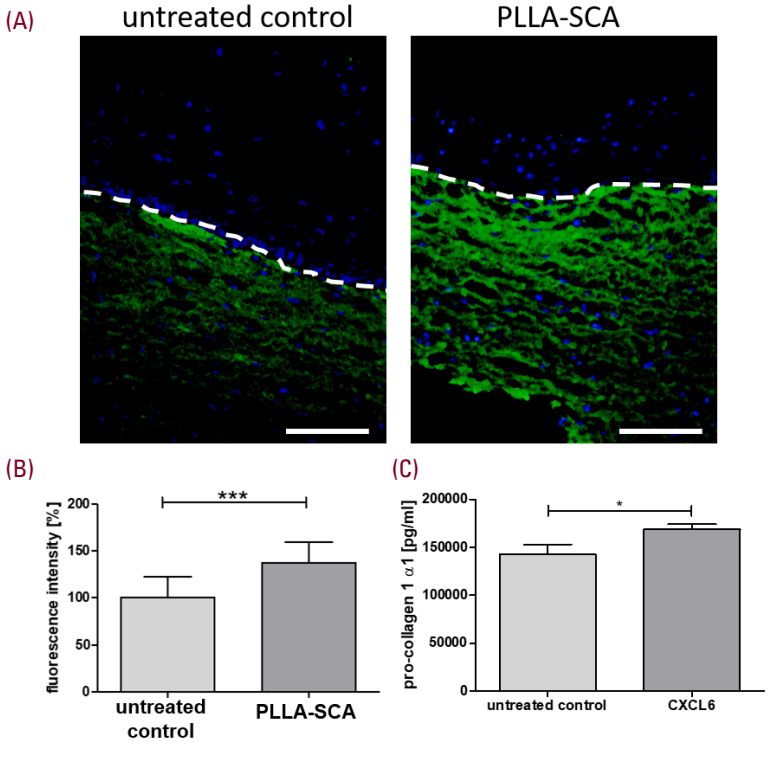


FIGURE 3. (A) Immunofluorescence examination of collagen I in 3D skin models on day 14 after PLLA-SCA injection. Untreated models served as controls. Representative images of three experiments are shown. The dashed line shows the basal membrane. (B) Quantification of fluorescence intensity, which was measured at five different representative positions per image of all experiments. ***P<0.001. (C) Pro-collagen I α1 ELISA of monolayer dermal fibroblasts that were stimulated with human recombinant CXCL6 (50 ng/ml).



Data are given as arithmetical means ± standard deviation; *P<0.05. Three independent experiments were performed.

DISCUSSION

Although several human and animal studies demonstrated the volume-enhancing effects of PLLA-SCA injections, the molecular biological effects of PLLA-SCA are only partially understood. The few in vitro studies to date on the efficacy of PLLA-SCA have used only monolayer cell cultures.[12] In our previous in vitro study, we found a stimulatory effect on epidermal thickness at day 5 after PLLA-SCA injection in full-thickness 3D skin models comprising fibroblasts and keratinocytes.[7] Gene expression profiling in these models revealed a PLLA-SCA-induced upregulation of integrins, laminins, and growth factors, among other genes.[7] Now, to investigate more deeply the biostimulatory effects of PLLA-SCA on collagen synthesis, we developed a new 3D skin model with incorporated macrophages, since it was shown that PLLA-SCA-dependent collagen production in fibroblasts occurs only in co-culture with macrophages.[12] In contrast to a previous in vitro study claiming a potentially unfavorable effect of PLLA-SCA fillers on fibroblast phenotype,[13] we did not observe any adverse effects of PLLA-SCA injection in our 3D skin models.

On days 5 and 14 after injection of PLLA-SCA into macrophage-containing skin models, we found an increased epidermal thickness at the histological level, consistent with our previous findings in 3D skin models without macrophages.[7]

On day 14 after PLLA-SCA injection, a gene expression profiling revealed an upregulation of genes expressing essential components of the dermal-epidermal junction (eg, integrins such as ITGA6, laminins such as LAMA3, and desmogleins such as DSG2). These data support the stimulatory effects of PLLA-SCA on the volume and integrity of the epidermis and especially the basement membrane. In this regard, it is interesting to note that a new study suggests a potential benefit of PLLA-SCA in the treatment of melasma where disorders of the basement membrane are involved.[14] Our data would support this potential use of PLLA-SCA in the treatment of melasma, especially by restoring basement membrane damage and upregulation of TGFb1 expression, which is known to decrease melanin synthesis via delayed extracellular signal-regulated kinase activation.[15] Further studies are needed to clarify this in detail.

Interestingly, immunohistochemical analyses exhibited a stimulatory effect of PLLA-SCA injection on collagen I production in our macrophage-containing skin models, which correlates to previous clinical findings.[16] This is the first time that these PLLA-SCA-dependent effects on collagen synthesis have been demonstrated in an in vitro 3D skin model. We assume that these effects could be attributed, at least in part, to the upregulation of IL1B and CXCL6 that we found in our gene expression analysis. In this context, previous studies indicated that CXCL6, which appears to be mainly induced by IL1B,[17] stimulates collagen synthesis in lung fibroblasts.[18] To substantiate our assumption, we have now shown for the first time that CXCL6 can also stimulate the synthesis of collagen I in dermal fibroblasts.

In summary, our data provide for the first time deeper molecular insights into the biostimulatory mode of operation of PLLA-SCA injections by performing a comprehensive in vitro study using 3D skin models containing macrophages.

DISCLOSURES

The authors have no conflicts of interest to declare.

ACKNOWLEDGMENT

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BRIEF COMMUNICATION

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Functional and Cutaneous Treatment Outcomes With Intravenous Immunoglobulin for Eosinophilic Fasciitis: A Retrospective Study

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ABSTRACT

Background: Eosinophilic Fasciitis (EF) is a rare subtype of deep morphea with an elevated risk of functional impairment. No treatment algorithm has been established for adults with EF refractory to traditional corticosteroid or immunomodulatory treatments. Research on cutaneous and functional outcomes of alternative therapies, such as intravenous immunoglobulin (IVIG), remains scarce.

Objective: To describe the functional and cutaneous outcomes associated with IVIG in adults with treatment-refractory EF at a tertiary referral center.

Methods: We performed a retrospective chart review of 18 consecutive patients with EF identified through a billing code search seen within the UCSF Department of Dermatology between 2015 and 2022.

Results: Seven patients (41.2%) underwent at least one course of intravenous immunoglobulins (IVIG) during the study period. Of 6 patients with available follow-up data, 5 patients (83.3%) achieved both sustained cutaneous and functional improvement. In the IVIG cohort, 1 patient (16.7%) achieved complete response with relapse, 4 (66.7%) were partial responders, and 1 (16.7%) was a non-responder who required treatment with mepolizumab. Adverse effects of IVIG included headaches in 1 patient (14.3%) and rash in 2 patients (28.6%). There were no reported veno-occlusive or thromboembolic events associated with IVIG.

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INTRODUCTION

Eosinophilic Fasciitis (EF) is a rare subtype of deep morphea characterized by progressive symmetric sclerosis of the fascia of the distal extremities with or without truncal involvement.[1] Joint contractures, myalgias, and reduced mobility are potential complications.[2,3] While oral corticosteroids remain first-line, almost half of EF patients require other immunosuppressants due to incomplete response or treatment intolerance.[3,4] The use of intravenous immunoglobulin (IVIG) in addition to standard immunosuppressive treatments has been described in a small retrospective cohort study and a few case reports, which reported IVIG treatment responses in adult patients with recalcitrant EF.[4,5,6] This retrospective observational study describes patient- and physician-reported cutaneous and functional outcomes for adults with EF treated with IVIG at a tertiary referral center.

MATERIALS AND METHODS

This IRB-approved study is a retrospective chart review of all adult patients with EF seen within the University of California San Francisco School of Medicine (UCSF) Department of Dermatology from 1/1/2015 to 6/13/2022. Patients with morphea were identified via a search of ICD-10 billing codes: morphea (L94.0) and eosinophilic fasciitis (M35.4). Authors B.O., W.F, and J.G. reviewed electronic health records to assess for clinical diagnosis of morphea. Author A.H. validated cases of diagnostic uncertainty. Data on demographics, morphea subtype, disease characteristics, treatment course, and response were reviewed. Patients were classified as complete responders, partial responders, or non-responders based on erythema and/or induration (resolved, decreased, or increased, respectively), new or expanding lesions (absent, absent, and present, respectively), functional impairment (significantly improving,

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TABLE 1.

Demographic Characteristics and Clinical Response of 6 Patients Treated With IVIG

Patient	Age[a]	Sex	IVIG Dose	Previous Systemic Treatments	# of IVIG Cycles Completed	Adverse Effects	Overall Clinical Response
1	61	F	2g/kg monthly divided over 4 days	MTX Oral Pred IV SSP	33	Urticaria	Complete responder followed by recurrence
2	26	F	N/A[b]	MTX Oral Pred HCQ Jak Inhibitor Cyclosporine	12	None	Non- responder
3	43	M	2g/kg monthly divided over 4 days	MTX Oral Pred Oral SSP	9	None	Partial responder
4	64	F	20g/200 mL subcutaneous ig at home	MTX Oral Pred	34	Headache and acral dyshidrotic reaction	Partial responder
5	81	F	2g/kg monthly divided over 4 days	MTX Oral Pred IV SSP	17	None	Partial responder
6	57	M	2g/kg monthly divided over 2 days	None	N/A[c]	None	Partial responder

[a]Value reflects age at start of IVIG therapy.
[b]Precise dosage unknown; patient received infusions outside of UCSF facilities.
[c]Unknown; patient treated with IVIG for an unrelated neurological diagnosis 2 years prior to treatment of EF.
Abbreviations: F = female, M = male, MTX = methotrexate, Pred = prednisone, SSP = systemic steroid pulse, HCQ = hydroxychloroquine

improving, or worsening, respectively) and physician clinical assessments (complete response, partial response, or non-response, respectively). Qualitative descriptions of cutaneous and functional outcomes were provided through chart notes.

RESULTS

Of 226 patients with morphea, we identified 18 patients (8.0%) with EF, of whom 6 patients (33.3%) had detailed IVIG follow-up data (Table 1). All patients had functional impairments prior to IVIG initiation. IVIG was administered with a corticosteroid and a steroid-sparing agent (SSA) in 5 patients (83.3%); 1 patient (16.7%) received a SSA only. While IVIG was never provided as a monotherapy, five patients (83.3%) discontinued oral corticosteroids while on IVIG. The average duration of IVIG therapy was 20.6 ± 16.4 months, and the standard IVIG dose was 2g/kg monthly divided over 2-4 days (Table 1).

Four patients (66.7%) reported both cutaneous and functional improvement within 2 months (Table 2). Both cutaneous and functional improvement were sustained across subsequent IVIG cycles in 5 patients (83.3%). Four patients (66.7%) were partial responders (Table 1). One patient (16.7%) achieved complete remission after 36.3 months of therapy; they relapsed with focal truncal involvement within 3 months of discontinuation, but without new functional deficits, and IVIG was not resumed. One patient (16.7%) was a non-responder with new lesions and persistent polyarthralgias who discontinued IVIG and achieved a partial response with mepolizumab. Adverse effects of IVIG included urticaria without systemic symptoms in 1 patient (16.7%) and headaches, malaise, and an acral dyshidrotic reaction in 1 patient (16.7%). No patients experienced a thromboembolic or veno-occlusive event.

TABLE 2.

Patient-Reported Clinical Outcomes of 6 Patients Treated With IVIG

Clinical Outcome	Number of patients (%)[a]
Function[a]	
Improved mobility	4 (66.7)
Improved range of motion	6 (100)
Reduced joint stiffness	2 (33.3)
Return to physical activity	2 (33.3)
Subjective endorsement of global improvement	4 (66.7)
Cutaneous	
Reduced skin tightness	3 (50.0)
Skin softening	3 (50.0)
Skin stability	2 (33.3)
Reduced skin stiffness	1 (16.7)
Reduced swelling	1 (16.7)

[a]Values may not add up to 100%, as an individual patient may have multiple findings within a category.

DISCUSSION

This study expands on limited available data supporting IVIG as a well-tolerated add-on therapy for patients with EF who suffer persistent cutaneous disease and functional impairment despite corticosteroids and SSAs. Although concomitant treatment with corticosteroids and SSAs may have reduced our ability to isolate the effects of IVIG, we emphasized careful comparison of patient and provider-reported clinical findings before, during, and after treatment courses with and without IVIG to thoroughly characterize its impact. While this small cohort study is limited by its retrospective nature and the rarity of EF, we present

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findings from the largest cohort of adults with EF treated with IVIG to date, offering additional support for the use of IVIG as an adjunctive treatment to traditional systemic therapies, particularly in recalcitrant cases.

DISCLOSURES

Author A.H. is a consultant to CSL Behring and Guidepoint LLC. Other authors have no conflicts to report.

IRB approval status: Reviewed and approved by UCSF Parnassus Committee; #348854.

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Expanding Inclusivity: Tranexamic Acid for the Treatment of Melasma in Males

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INTRODUCTION

Tranexamic acid (TXA) is an antifibrinolytic medication largely known for its efficacy in managing menorrhagia, or heavy periods, making it a medication predominantly used by women. It was first used in the 1960s, and by the 1970s, early studies revealed tranexamic acid's effectiveness in reducing excessive menstrual bleeding.[1] TXA is now a standard for treating menorrhagia.

More recently, TXA has found a new dermatologic purpose for the improvement of any melasma-related pigmentation. Melasma is a skin condition commonly characterized by dark patches or irregularities in pigmentation in the skin, particularly in sun-exposed areas.[2,3] Subsequent studies have shown promising results in TXA's effectiveness in reducing melanogenesis, the process by which pigment in the skin and hair is produced.[4] Although, many of these studies largely focus on female populations, leaving male melasma patients in the minority. The historical background of the drug's initial use could largely be the reason why there are so few male patients included in current studies. Melasma can negatively impact an individual's self-esteem and confidence thereby reducing the quality of life of an individual.[5] We hope to shine a light on the efficacious nature of oral TXA on male melasma patients. We now consider oral TXA for all melasma patients, male and female, before undergoing any additional treatments with lasers or chemical peels.

CASES

Case 1:

This is a 45-year-old male with moderate melasma on his face and neck. He was started on a regimen of oral tranexamic acid 650 mg daily, along with topical tretinoin 0.05% gel every evening and topical tranexamic acid 3% serum (Discoloration Defense by Skinceuticals, New York, NY) twice daily, along with daily physical sunblock. He received four treatments of KTP vascular laser (ExcelV by Cutera, Brisbane, CA). Almost complete resolution was achieved about 14 months from the first appointment. He has maintained his results with the same oral and topical regimen as of publication.

FIGURE 1. Case 1, pre-treatment.

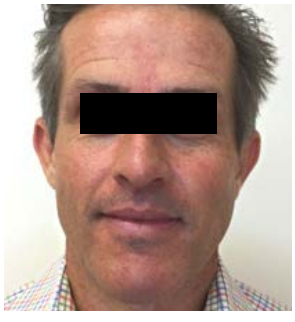


FIGURE 2. Case 1, post-treatment.

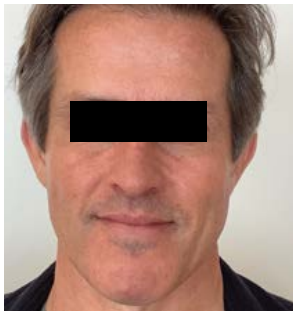
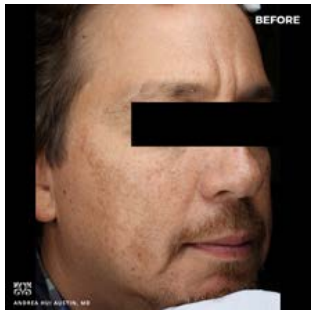


FIGURE 3. Case 2, pre-treatment.



Case 2:

This is a 55-year-old man with moderate melasma and also a self-described outdoorsman and surfer. He was often tanned and not a candidate for laser. He was started on a regimen of oral tranexamic acid 650 mg daily and topical compounded

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FIGURE 4. Case 2, post-treatment.

tretinoin 0.025%/hydroquinone 4%/hydrocortisone 0.5%/kojic acid 6% by Sincerus Pharmaceuticals, Pompano Beach, FL) every evening. He received a series of 6 chemical peels (Vitalize peel by Allergan, Irvine, CA) with complete resolution of his melasma.

Case 3:
This 56-year-old gentleman had a combination of severe melasma superimposed with sun damage. He began a regimen of oral tranexamic acid 650 mg daily, along with topical retinol 1% (AlphaRet by SkinBetter Science, Phoenix, AZ) every evening along with physical sunblock daily. He received two chemical peels (Vitalize peel by Allergan, Irvine, CA) and two treatments of Q-switched Alexandrite laser (Alex Trivantage by Candela, Marlborough, MA) with near-complete resolution. He has maintained his results with the same oral and topical regimen as of publication.

FIGURE 5. Case 3, pre-treatment.

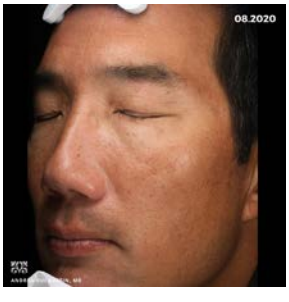

FIGURE 6. Case 3, post-treatment.

DISCUSSION

Melasma is a common, acquired skin condition that can be caused by a multitude of factors including genetics, radiation, hormones, cosmetics, and phototoxic drug usage.[6] TXA can be administered for all severities of melasma. The exact mechanism for how TXA reduces melanogenesis is not yet fully understood. What we believe is a probable explanation for its effectiveness is TXA's ability to inhibit the activity of plasmin. Plasmin can stimulate melanocytes, the cells that are responsible for producing melanin. By inhibiting plasmin, TXA can reduce the stimulation of melanocytes thus decreasing melanin synthesis.[7] TXA may also be involved with the interference of melanin synthesis. TXA is structurally similar to tyrosinase, an enzyme that plays a crucial role in melanin production and may work by competitively antagonizing its function.[3] Additionally, it has been found that TXA has anti-inflammatory properties and can modulate the inflammatory response by influencing cytokine levels.[8] Normally, chronic inflammation can trigger melanogenesis and contribute to hyperpigmentation. Thereby, with the reduction of this inflammation, TXA can indirectly inhibit melanin production. While more research is needed to fully understand the exact mechanisms behind TXA's dermatologic effectiveness, TXA has brought great success in the many melasma patients we have seen.

There are a few studies in the current literature that support the use of TXA in treating melasma, although currently, there are no studies that only focus on men. Even so, when studies do include a male population, few males make up a portion of the sample size. In one of the largest studies of oral TXA, 561 patients were enrolled, while only 8.6% of those patients were male. The majority of patients found an improvement in their melasma symptoms.[9] A randomized controlled trial of 96 patients compared the effect of TXA on intraoperative blood loss (IOB) based on gender. Interestingly, it was found that there was an effect in women, but none in men. However, the paper noted that future studies should include larger sample sizes of men.[10] All in all, within current literature, it is clear that there is no consensus when it comes to TXA and men.

TXA is effective at treating melasma. One randomized controlled trial compared 20 patients taking 250 mg TXA twice a day and 17 patients receiving the placebo for 12 weeks. They found that melasma improved in 50% of the patients in the experimental group versus only 5.9% in the placebo group.[11] Another trial compared a group of 18 taking the same dosage as the previous study, with 21 patients taking the placebo. Only the group taking TXA saw significant improvement.[12]

TXA also has a well-established safety profile. Previous studies have reported adverse side effects associated with TXA, however, we must note that these negative side effects occurred at significantly higher doses than what our findings suggest as

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effective for treating melasma. The most commonly reported side effects include menstrual changes, nausea, gastritis, back pain, and headaches.[11] In a controlled study of patients with melasma, a dosage of 250 mg of oral TXA given twice daily for 3 months revealed no serious adverse side effects. There were also no statistically significant differences in side effects between the TXA group and placebo group.[12] Within our practice, with over 1500 prescriptions (not including refills) of oral tranexamic acid written, we have only seen two cases of venous thrombosis with extenuating circumstances that exacerbated the possible side effects.

Overall, TXA taken orally at 650 mg daily provides patients with a significant reduction of their melasma. Research on this subject heavily focuses on female subjects and a majority of sample sizes make up females in these studies. While melasma predominantly affects women, it is important to acknowledge the impact that it has on men as well. Tranexamic acid has shown to be efficacious in our male melasma patients, and we hope that more men are offered this treatment method to target their melasma. As research continues to explore the applications of tranexamic acid, practitioners should consider the addition of oral TXA into the treatment plans for male melasma patients, as it has shown to be safe and seems effective based on our experience.

DISCLOSURES

The authors have no disclosures or conflicts.

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Analysis of Utilization, Cost, and Prescription Trends of Common Immunosuppressive Medications Among Medicare Patients 2013 to 2019

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INTRODUCTION

Immunosuppressive medications are commonly used to manage dermatological conditions, including atopic dermatitis, psoriasis, and bullous diseases. However, cost and adverse effect profile, including increased risk of infections, are important considerations.[1] Despite their widespread use, literature on the cost and utilization trends of common immunosuppressives used for dermatological treatment is sparse. A comprehensive understanding of these trends is essential for dermatologists, patients, and policymakers when deciding upon treatment options. Therefore, we sought to analyze the utilization, cost, and prescription trends of common immunosuppressive medications used in dermatology in the Medicare population.

We performed a cross-sectional analysis of the 2013 to 2019 Medicare Part D Provider utilization and payment data sets to identify prescription claims filed by dermatologists for azathioprine, cyclosporine, methotrexate, prednisone, hydroxychloroquine, mycophenolate, and methylprednisolone. Other provider types were excluded. Statistical Package for the Social Sciences (SPSS) was used to perform data analysis. Primary outcomes were total annual claims, cost, and supply days per 100,000 Medicare Part D beneficiaries for each immunosuppressive agent. The total cost per supply day was calculated by dividing the total drug cost by the total drug supply days.

Prednisone claims increased by 6.6% (Table 2), in conjunction with a 25.7% increase in cost per supply day (Table 1), with total spending increasing by 53.5%. Methylprednisolone total spending decreased by 55.7% during the study period, corresponding with a 45.6% decrease in cost per supply day (Table 1), and a 15.1% decrease in the total number of claims (Table 2). Methotrexate claims increased by 13.4%, with total spending decreasing by 25.8% in 2013-2019 (Table 2). The decrease in cost per supply day ($1.48 to $0.88) (Table 1) outpaced the corresponding increase in prescription claims.

Azathioprine claims increased by 45.0% with total spending increasing by 125.2% (Table 2). Cyclosporine claims increased by 52.6% with total spending increasing by 92.9% since 2013 (Table 2). Although the cost per supply day increased at a faster rate for azathioprine compared with cyclosporine, cyclosporine was more than 10 times more expensive than azathioprine ($1.30 vs $16.22) (Table 1).

Overall, there was an increase in total claims for immunosuppressives prescribed by dermatologists over the study period. This might be because some insurance companies have established fourth-tier plans, with coinsurance payments of up to 40% rather than a fixed copayment for high-cost specialty medications (such as biologic medications), causing significant financial burdens for patients with complex chronic illnesses, and forcing dermatologists to prescribe cheaper alternatives.[2]

TABLE 1.

Cost Per Supply Day of Non-Biologic Immunosuppressive Therapy

Year	Prednisone	Methyl-Prednisolone	Methotrexate	Hydroxy-Chloroquine	Myco-Phenolate	Azathioprine	Cyclosporine
2013	0.25	3.33	1.48	0.49	5.20	0.85	13.62
2014	0.38	3.12	1.65	0.76	4.61	0.89	9.30
2015	0.38	2.86	1.59	3.70	3.08	1.21	10.84
2016	0.36	2.51	1.24	3.34	2.69	1.07	11.48
2017	0.36	2.13	1.35	3.25	3.04	1.40	15.44
2018	0.35	1.94	1.16	2.50	3.11	1.32	19.21
2019	0.34	1.81	0.88	1.96	3.34	1.30	16.22

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TABLE 2.

Total Number of Claims, Drug Supply Days, and Cost of Non-Biologic Immunosuppressive Therapy							
Year	Prednisone	Methyl-Prednisolone	Methotrexate	Hydroxy-Chloroquine	Myco-Phenolate	Azathioprine	Cyclosporine
Total Number of Claims							
2013	27.49	26.49	32.34	21.16	21.69	18.48	14.80
2014	28.19	25.93	32.06	22.72	21.90	18.75	17.38
2015	29.08	26.44	33.2	22.74	22.86	19.97	18.25
2016	28.84	27.24	35.18	23.37	22.66	19.69	16.63
2017	29.38	25.63	35.20	22.95	22.55	21.44	16.67
2018	30.13	24.62	36.53	22.97	22.65	22.93	15.11
2019	30.08	22.50	36.77	23.03	23.64	24.23	22.58
Total Drug Supply Days							
2013	641.16	254.36	1165.16	858.48	751.04	680.41	456.80
2014	674.24	227.84	1168.85	878.87	756.23	693.99	565.63
2015	698.73	230.33	1225.47	883.99	812.11	736.62	605.00
2016	697.63	249.96	1280.84	926.93	806.22	716.61	498.88
2017	711.79	232.66	1301.34	933.49	826.55	796.88	500.44
2018	724.90	218.87	1397.77	982.48	856.42	885.53	447.11
2019	725.50	187.56	1461.64	1065.60	907.63	978.54	713.0
Total Cost, $							
2013	144.47	715.86	1696.58	407.04	3291.80	547.40	5885.64
2014	228.68	608.65	1927.28	659.81	2816.11	582.59	5738.40
2015	234.10	559.03	1920.15	3183.17	2445.66	866.49	6938.35
2016	224.79	567.06	1574.78	3019.43	2179.89	780.01	6182.01
2017	231.46	449.16	1728.39	2976.96	2297.52	1070.85	7872.21
2018	228.29	408.64	1586.52	2412.10	2481.04	1187.94	8476.09
2019	221.81	317.18	1259.03	2007.09	2889.38	1232.91	11356.54

Methotrexate claims increased over the study period. In a cost modeling study analyzing annual trends in Average Wholesale Prices (AWP) for psoriasis medications from 2000 to 2008, annual costs ranged from $1197 for methotrexate to $27,577 for alefacept, with an average AWP increase of 66% for all psoriasis therapies.[3] A 2017 cross-sectional comparative policy study found that in 2013, the United States, in comparison to other countries, had historically low generic drug prices and high rates of generic drug use (84%), which may have led to increased competition among generic and brand-name drug manufacturers.[4] Therefore, the increase in methotrexate claims that we observed might be because methotrexate is the most cost-effective psoriasis treatment, in addition to heightened drug manufacturer competition lowering methotrexate costs.

The total number of claims and price of methylprednisolone decreased over the study period, which might be due to the approval of alternative treatments, such as dupilumab for atopic dermatitis in 2017[5] and rituximab for pemphigus vulgaris in 2018.[6] In contrast, prednisone claims increased likely because it is used more extensively across a broader range of dermatological conditions.

Limitations include retrospective design and including only Medicare patients. This cohort may not be representative of the general population and other time periods, preventing the generalizability of results. Furthermore, our analysis focused on prescription claims data, which may not represent medication utilization due to non-adherence or medications obtained through alternative sources.

In sum, we found an overall increase in total claims for non-biologic immunosuppressive therapies prescribed by dermatologists among Medicare beneficiaries from 2013 to 2019, which might be due to insurance plan restrictions and the financial burdens of newer, more expensive treatments. Since costs and claims of immunosuppressants vary over time, dermatologists, patients, and policymakers must stay updated on these trends to make informed decisions that will ultimately optimize resource allocation and improve patient outcomes.

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DISCLOSURES

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LETTERS TO THE EDITOR

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Clinical Impacts of Omalizumab on the Psychiatric Comorbidities of Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis

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INTRODUCTION

Individuals with chronic spontaneous urticaria (CSU) experience significant sleep disturbances and are at risk of anxiety and depression.[1] There is strong evidence supporting the use of omalizumab in the management of CSU.[2] Clinical impacts of omalizumab on the cutaneous symptoms of CSU have been widely investigated, but its impact on the psychiatric comorbidities of CSU remains unclear.[3] The objective of this systematic review and meta-analysis is to determine the clinical impacts of omalizumab on depression, anxiety, and sleep in patients with CSU.

Our study protocol was pre-registered on PROSPERO (CRD42021272707). Medline, Embase, and CENTRAL were searched from inception to April 20th, 2022, using the keywords "urticaria" and "anxiety"/"depression"/"sleep". Of 200 records, seven studies totaling 1,398 patients were included (71% female, age range of means 44.6 to 46.4 years). All studies were of fair or good quality and low risk of bias. Standardized mean difference (SMD) combined disparate scales, with 0.2, 0.5, and 0.8 representing small, moderate, and large SMDs, respectively.[4]

Across three studies totaling 124 patients with CSU, treatment with omalizumab was associated with a large decrease in depression scores (SMD=1.07, 95%CI 0.68-1.46, P<0.001) from baseline (Figure 1). Patients on omalizumab demonstrated a large, clinically meaningful reduction in depressive symptoms (17.5% reduction in Beck Depression Inventory), irrespective of their cutaneous response. In one randomized controlled trial (RCT) of 68 patients with CSU, patients receiving omalizumab were significantly more likely to no longer meet the clinical criteria for depression at 28 weeks (OR 5.55, 95%CI 1.7-18.2, P=0.005) compared to placebo.

Across two studies totaling 257 patients with CSU, treatment with omalizumab was associated with a large decrease in anxiety scores (SMD=1.00, 95% CI 0.72-1.27, P<0.001) from baseline. Across three RCTs totaling 975 patients with CSU, treatment with omalizumab resulted in a moderate improvement in sleep quality at 12 weeks (SMD=0.43, 95% CI 0.34-0.53, P=0.001) compared to placebo. Of note, CSU patients on 300 mg of omalizumab every 4 weeks had the best response (test for subgroup differences: P=0.06, I^2=65.1%).

The association between CSU and psychiatric comorbidities is likely multifactorial. In addition to increased counts and degranulation of mast cells and basophils in CSU, patients with depression also demonstrate increased TNF-α and interleukin-6 levels.[5] Omalizumab binds to free IgE to inhibit mast cell degranulation and prevent the release of pro-inflammatory cytokines, including TNF-α and interleukin-6.[1] This reduction in pro-inflammatory cytokines, along with a reduction in cutaneous symptoms, likely contributed to the improvement of psychiatric comorbidities in patients with CSU treated with omalizumab.[3] The alleviation of psychiatric comorbidities of CSU by omalizumab, independent of the patient's cutaneous response, further supports this. This review is limited by the paucity of randomized, placebo-controlled studies, and further controlled studies are needed to support its use for managing the psychiatric comorbidities of CSU.

In conclusion, this review lends further support to the use of omalizumab in the management of moderate-to-severe CSU. Patients with CSU receiving omalizumab reported markedly improved symptoms of depression, anxiety, and sleep disturbances, and were more likely to have resolution of CSU-associated depression. Furthermore, omalizumab was found to be effective in reducing the psychiatric impacts of CSU on patients, independent of their cutaneous response. Thus, clinicians may wish to consider the use of omalizumab as an effective treatment not only for the cutaneous symptoms of CSU, but also for the psychiatric comorbidities resulting from this disease.

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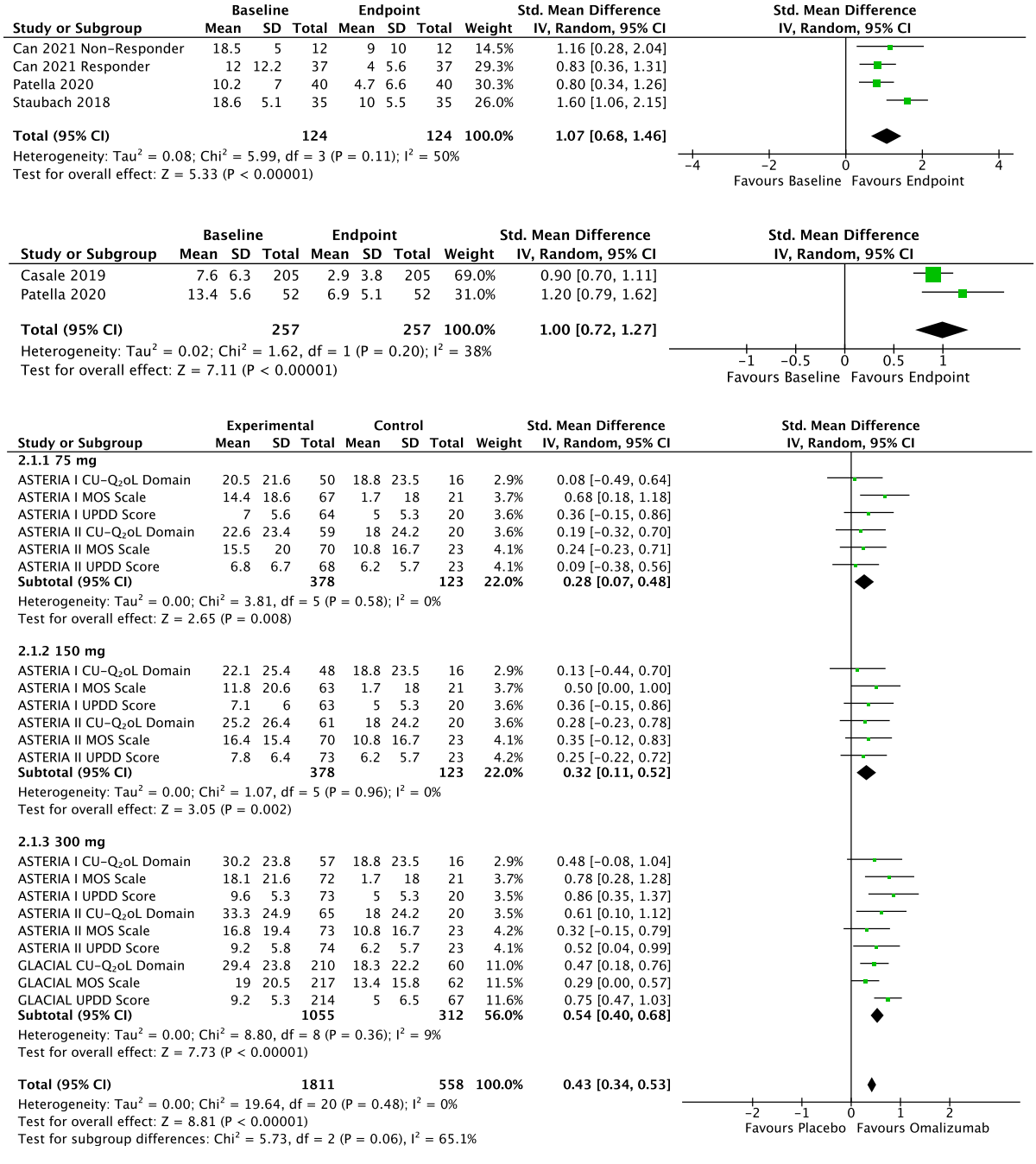
FIGURE 1. Forest plot showing the improvement in depression (top panel), anxiety (middle panel), and sleep disturbance (bottom panel, various doses) scores across studies in patients receiving omalizumab compared to baseline or placebo at study endpoint.



DISCLOSURES

The authors have no conflicts of interest to declare.

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LETTERS TO THE EDITOR

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Expression of IL-4 in Tumors: A Safety Surrogate to Predict Cancer Survival Associated With Biologic Therapies

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INTRODUCTION

Interleukin (IL)-4-targeted therapies have revolutionized management of inflammatory dermatoses. Dupilumab, an IL-4 receptor alpha inhibitor, is approved for moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis[1] with ongoing studies including in urticaria, prurigo nodularis, and alopecia.[2] Interleukins are critical mediators of immunosurveillance, and a theoretical increased risk of malignancy exists for any interleukin inhibitor until real-world long-term safety data are explored. Genomic expression studies can help examine if interleukin deficiencies are associated with increased malignancy risk, providing a proxy for long-term interleukin repression.

We utilize data from the Cancer Genome Atlas to investigate if IL-4 expression is correlated with overall survival (OS) in

TABLE 1.

Survival Harm Odds Ratio (OR) With Low IL-4 Expression			
Cancer (n=)	**n**	**OR (high exp=ref)**	***P*-value***
Pheochromocytoma/paraganglioma	184	0.46 [0.11-1.93]	0.291
Adrenocortical CA	77	0.55 [0.22-1.37]	0.198
Brain lower grade glioma	527	0.61 [0.40-0.95]	0.028
Renal cell carcinoma	531	0.74 [0.51-1.09]	0.133
Acute myeloid leukemia	163	0.82 [0.53-1.27]	0.377
Head and Neck CA	521	0.87 [0.55-1.37]	0.542
Glioblastoma multiforme	171	0.87 [0.58-1.31]	0.511
Hepatocellular carcinoma	346	0.87 [0.45-1.69]	0.690
Breast invasive CA	1076	0.90 [0.59-1.38]	0.640
Lung SCC	485	0.94 [0.64-1.37]	0.738
Renal papillary CA	286	0.94 [0.48-1.86]	0.866
Stomach adenocarcinoma	382	0.95 [0.67-1.35]	0.774
Uveal melanoma	80	1.01 [0.29-3.55]	0.988
Bladder CA	405	1.06 [0.69-1.63]	0.790
Colon adenocarcinoma	189	1.09 [0.42-2.84]	0.854
Lung adenocarcinoma	480	1.10 [0.78-1.56]	0.583
Endometrial CA	369	1.12 [0.65-1.95]	0.679
Esophageal CA	162	1.15 [0.61-2.19]	0.661
Cutaneous melanoma	430	1.36 [0.89-2.07]	0.158
Ovarian serous CA	293	1.43 [0.95-2.17]	0.087
Cervical CA	295	1.53 [0.70-3.35]	0.283
Sarcoma	262	1.82 [1.11-2.97]	0.018 (p_{adj}=0.2479)
Pancreatic adenocarcinoma	177	1.94 [1.12-3.37]	0.018 (p_{adj}=0.2479)
Thymoma	119	1.98 [0.46-8.50]	0.358
Thyroid carcinoma	507	2.72 [0.61-12.10]	0.188

Abbreviations: CA, carcinoma
**P*-value adjusted using False Discovery Rate (FDR)

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multiple cancers. After excluding cohorts with <10th percentile of patients, 25 malignancies were evaluated (n=8517). We used odds ratio to model OS with IL-4 expression (high/low, split by median expression value). Multiple testing correction was addressed with highly-conservative false discovery rate (FDR) P-value correction to the results of the multivariate hazards models, adjusted for sex, age at diagnosis, and tumor stage. Sensitivity analyses were performed with IL-4R (receptor) and IL-13. We found no significant adverse survival effects with IL-4, IL-4R, nor IL-13 expression in the examined cohorts.

IL-4 signaling blockade can lead to enhanced functioning of interferon-γ (IFNγ) producing cells.[3] Previous reports reveal extensive anti-tumor effects of IFNγ in bladder carcinoma, colorectal carcinoma, ovarian carcinoma, and adult T-cell lymphoma.[4] IFNγ can enhance the cytotoxic function of natural killer cells and cytotoxic T cells, increase the antigenicity of tumor cells by up-regulation of major histocompatibility complex class I, induce expression of p21 and p27 molecules to inhibit cell proliferation, and regulate PD-L1 expression on the surface of cancer cells. Furthermore, IFNγ-deficient mice are more susceptible to spontaneous neoplasms[5] and low IFNγ expression is a poor prognostic factor in ovarian carcinoma and melanoma. Our findings provide further support that dupilumab is unlikely to be associated with an increased malignancy risk. Limitations include that IL-4 expression levels are unlikely to directly correlate with a dupilumab-treatment phenotype. Additionally, we focus on individual expression of single cytokines, while pathways often involve complex changes in expression of multiple genes. Further prospective work is needed to continually assess the dupilumab safety profile.

DISCLOSURES

JFM was a consultant and/or investigator for Amgen, BMS, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma. NK was previously a consultant for BeiGene. JSS was a consultant and/or investigator for Biogen. LPC has no disclosures. CG has no disclosures.

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Advancing Dermatology Education and Care in Rwanda: The Impact of a New Academic Partnership

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Dear Editor,

This past spring the inaugural class, now fifth-year medical students, at The University of Global Health Equity (UGHE) in Butaro, Rwanda entered their sub-specialty training in Dermatology. UGHE is the result of visionary leadership from the late Dr. Paul Farmer and Partners in Health (PIH), the Cummings Foundation, and the Bill & Melinda Gates Foundation. It is the realization of a long-dreamed aspiration to create a university that would advance global health delivery by training a new generation of global health leaders who are equipped to not just build, but sustain effective and equitable health systems.

While PIH has many academic partners, creating an academic institution dedicated to health equity located in an environment where health disparities are most acutely felt was the ultimate goal. Students at UGHE, through a rigorous selection process, will complete a six-and-a-half-year program eventually obtaining a joint Medical Degree and Masters of Global Health where upon graduation, the students serve at least six years in a public district hospital as a doctor for a vulnerable population. UGHE's classes are purposefully 2/3 female to address gender inequality and the tuition is free. The graduating classes of 2025 and 2026 are entirely Rwandan but the following classes include students from Uganda, Burundi, Lesotho, Sierra Leone, Malawi, and Liberia with the intent to train future physicians who will be leaders and serve populations all over Africa.

Though Rwanda has a population of 13 million, there are only 12 registered board-certified dermatologists in the entire country, all of whom are located in the capital city of Kigali. Thus, the graduates must be equipped with sufficient dermatologic skills to diagnose and treat common conditions and understand when to refer from their respective rural communities. After three years of development, the dermatology curriculum commenced at UGHE with great success. In planning the dermatology clerkship and needing to teach the students on-site in Butaro, a dermatology clinic was established at Butaro District Hospital-

FIGURE 1. Dr. Ariel Eber demonstrates dermatologic procedural skills including biopsies, excisions, and bedside diagnostics on site at the campus of UGHE.

the teaching site of UGHE. In doing so, dermatologic care was newly made available to the northern province, a community of 1.2 million, who previously had to travel over two hours to Kigali. A new wing in the Butaro District Hospital has been built and opened in late 2023. The Hospital leadership has recognized the need to expand dermatology care and is building a small dermatology clinic space in this new hospital.

Visiting faculty from partner institutions this year traveled from across the United States for a week at a time to teach the incredibly inspiring and eager students of UGHE alongside local dermatologist Dr. Jean Bosco Ndagijimana. There are also over 15 virtual faculty. Currently, UGHE is inviting volunteer senior Residents, Fellows, and Board-certified Dermatologists for the Spring 2024 clerkship. There are opportunities to participate virtually or in person. Support for this clerkship has been generously provided by both the American Academy of Dermatology and Galderma.

DISCLOSURES

The authors have no conflicts of interest to declare.

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LETTERS TO THE EDITOR

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Analysis of Reddit Reveals JAK Inhibitor Questions Among Atopic Dermatitis Patients

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ABSTRACT

Reddit is a popular social media website that is increasingly being used as a source of health information and discussion, especially among the younger population. We analyzed the subreddit "eczeJAKs" (a group whose "about" statement is: "Janus Kinase Inhibitors for Th2 Dermatitis"), and found many gaps in patient knowledge, showing areas for future improvement.

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INTRODUCTION

Reddit is the 7th most visited site in the United States (US) and has become an popular forum for health-related discussions.[1] According to a 2021 study, users ages 10-19 comprise 21% of Reddit users, with nearly half of users being under the age of 29.[2] Furthermore, users seeking health-related information on Reddit are among the most likely to enact the information in their lives.[3]

Approximately 13% of children in the US have atopic dermatitis (AD).4 Patients with AD are known to heavily engage on Reddit, forming subreddits, or specific discussion boards related to distinct AD topics.[1] With the recent FDA approval of Janus kinase inhibitors (JAKi) for AD treatment, a subreddit was formed on January 16, 2020. The analysis of a subreddit can provide physicians with valuable information regarding patient care.[1] By familiarizing oneself with concerns expressed on a widely utilized social media platform, physicians can gain additional insight into the patient's perspective about treatment and use this information to strengthen anticipatory guidance, counseling, and the patient-provider relationship.

MATERIALS AND METHODS

The authors analyzed all 219 posts on the "eczeJAKs" subreddit (a group whose "about" statement is: "Janus Kinase Inhibitors for Th2 Dermatitis"), which has 1,006 subscribers as of May 28, 2023. Each post was placed into one of 15 categories (Table 1).

DISCUSSION

Our analysis of the "eczeJAKs" subreddit demonstrates helpful data regarding the AD patient experience on JAKi, highlighting patient gaps in knowledge that physicians can improve on. The highest proportion of posts was questions in the general experience category, followed by side effects. Therefore, we suggest that physicians emphasize potential side effects when taking JAKi. To date, the most common reported adverse effects of oral JAKi are upper respiratory infections, nasopharyngitis, nausea, headache, and acne.[5] Providers could also emphasize that itch-relief can be seen as early as the first 24 hours of treatment.[5]

Surprisingly, we found a number of undocumented side effects described in the posts. While these side effects may offer a broader patient perspective, they are difficult to classify and

TABLE 1.

The Proportion of Posts by Category

Category	Number (N=219)	%
Side effects	36	16.4%
Usage Instructions	17	7.8%
General Experience	60	27.4%
Efficacy	15	6.8%
Insurance Coverage and Finances	12	5.5%
Concurrent Use with Other Medical Interventions	3	1.4%
Obtaining prescription	13	5.9%
Timeline for Symptom Improvement	5	2.3%
Miscellaneous	9	4.1%
Updates to Medication via Clinical Trials, News, and Media	28	12.8%
Fear/Concern	9	4.1%
Mental Health	3	1.4%
Patient-Provider Relationship	4	1.8%
Tobacco/Alcohol	2	0.9%
Covid	3	1.4%

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TABLE 2.

Example of Posts by Category and Subcategory

Category	Subcategory	Example Post Title	Example Post Excerpt
General Experience	Topical Steroid Withdrawal	opzelura: getting these weird bumps after i stopped using opzelura after they cleared (the instructions say to stop using when clear). is anyone else experiencing this? I feel like my skin is getting addicted to it like with steroids :((	Photo of Rash
Usage Instructions	N/A	Rinvoq twice daily?	"Hey all, I am on Rinvoq 30mg/once daily for AD. I am wondering if anyone has any input about splitting this pill between two times of the day?"
Updates to Medication via Clinical Trials, News, and Media	Clinical Trial	Can't use grape fruit during trial...	Hey to whoever is reading this, I've been in a study for about a year now for upadacitinib and my skin has been doing good but as I was reading the consent form I came across it saying that "consumption of grape fruit or grape fruit juice may affect levels of upadacitinib and increase risk of side effect" Can anyone explain how grape fruit does this effects the levels and does it include oranges as well??
	News/Media	US Congresswoman questions Abbvie (Rinvoq) CEO on shady corporate practices	Link to Video of Congresswomen
Side Effects	Conjunctivitis	Eye Issues	Anyone have any eye issue develop or any eye issues solved since switching to JAKS?
	Upper Respiratory Infection	Stopping RINVOQ for a week due to an infection	I have to take antibiotics for an infection and need to temporarily stop RINVOQ. I was wondering if anyone else has stopped RINVOQ for a short period. Did you flare up? Did it work again after restarting treatment?
	Muscle Pain	Can anyone help me with Rinvoq?	Was on Rinvoq 30mg a day for about 2 months and started with bad RANDOM aches all over my body especially my right leg, soles of my feet and back and shoulders (feels like bone pain). Sort of like twinges and stuff but finding it hard to function on a day to day basis or put full weight on my right leg and tiredness. Has anyone else experienced this I know its a long shot but worth a ask.
	Fatigue	Rinvoq and fatigue	Anyone experienced fatigue as a side effect while starting rinvoq? I've been on it for a week and I'm wondering if the fatigue will go away.
Fear/Concern	Cancer	Cibinqo (abrocitinib) cancer concerns?	However my only concern about cibinqo is my doctor warned me that there's a small potential chance it may increase risk of cancer? Has anyone else been warned of that in their clinical trial testing or their doctor or have heard of what percent of their test subjects got cancer? I tried googling and there's very minimal articles that mention some risk of lymphoma or skin cancer which worries me a bit.

should be interpreted with caution given the lack of verification methods. It is possible that some mentioned side effects will appear in pooled forums before more conventional clinical awareness develops. For example, text-mining of online healthcare forums can identify novel side effects, helping target post-marketing drug surveillance.[6]

Mentioned side effects not included in the prescribing information for JAKis include depression, delayed wound healing, and gynecomastia. Delayed wound healing may be plausible given the growth factors and cytokines necessary for wound healing utilizing the JAK/STAT intracellular signaling pathway for gene transcription.[7]

Regarding the general usage instructions category, many posts centered on the shingles vaccine, pointing to an area that may require greater clarification from physicians. Similarly, a post mentioned grapefruit usage in a clinical trial, suggesting that physicians may need to elaborate on dietary issues. Notably, prescribing information for upadacitnib recommends that

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physicians advise their patients against the consumption of grapefruit as increased levels of the drug occur when co-administered with strong cytochrome 34A inhibitors (grapefruit, ketoconazole, clarithromycin), raising the risk of adverse reactions.[8]

Finally, we came across a significant number of posts expressing widespread unease and doubt about JAKis. Despite shared decision-making and anticipatory guidance, it appears that there is still a great deal of trepidation surrounding these medications.

CONCLUSION

The "eczeJAKs" subreddit has undergone substantial growth since its creation. We expect this subreddit to continue growing as JAKi use increases for AD. Misinformation can easily spread given the posts are not verified by health professionals With such a high number of youths using social media, there is concern that the shift towards health-focused social media may weaken the patient-provider relationship and create mistrust towards conventional medicine, as in topical steroid withdrawal syndrome.[9]

Furthermore, we believe that a significant amount of posts could have been prevented with greater patient education. A common theme throughout the subreddit was lack of proper time given from the dermatologist or the dermatologist being too busy to answer follow-up questions. Such concerns call for solutions that may entail interdisciplinary collaboration, online patient portals, patient support groups or advocacy organizations, better online education resources, and for better or for worse, even the use of artificial intelligence in the future.[10]

DISCLOSURES

D. Lio reports research grants/funding from AbbVie, AOBiome, and Regeneron/Sanofi Genzyme; is on the speaker's bureau for AbbVie, Eli Lilly, Galderma, Hyphens, Incyte, LEO Pharma, L'Oreal, MyOR Diagnostics, ParentMD, Pfizer, and Regeneron/Sanofi Genzyme; and reports consulting/advisory boards for AbbVie, Almirall, Amyris, AOBiome, Arbonne, ASLAN Pharmaceuticals, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosciences (stock options), Dermavant, Eli Lilly, Exeltis, Galderma, IntraDerm, Johnson & Johnson, LEO Pharma, L'Oreal, Menlo Therapeutics, Micreos (stock options), Pfizer, Pierre-Fabre, Regeneron/Sanofi Genzyme, Theraplex, and Unilever. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid, and is a Board member and Scientific Ad visory Committee Member of the National Eczema Association. Kripa Ahuja reports no conflict of interest. Grace DeSena reports no conflict of interest.

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FEATURED CONTENT

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NEWS, VIEWS, & REVIEWS

Antihyperglycemic Medication to Combat Skin AGE-ing

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INTRODUCTION

A multifactorial and complex process, aging is defined as the culmination over time of damage in cells and tissues resulting in altered function of an organism. Intrinsic and inevitable, the aging process impacts every organ of the human body, including the skin, leading to age-related diseases and ultimately death. Oxidative stress, cellular senescence, chronic inflammation, and the accumulation of metabolic waste products are major contributing factors to aging.[1] Skin aging affects not only its protective mechanical and immunological functions but also its aesthetic appearance. Two antihyperglycemic drugs, metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have garnered interest for their geroprotective properties.[2,3] The review herein will summarize the mechanisms underlying how these drugs may be protective specifically against skin aging.

Pathogenesis of Skin Aging

Defining features of aged skin are decreased elasticity, epidermal atrophy, dyschromia, and xerosis.[4] A main intrinsic factor of skin aging is the decline of estrogen and androgen levels over time, while the primary extrinsic factor is exposure to ultraviolet radiation (UVR).[5] Common to both intrinsic (chronological) and UVR-induced skin aging is the increased generation of reactive oxygen species (ROS) and DNA damage. Both products lead to increased induction of matrix metalloproteinases (MMPs), thereby increasing degradation of collagen and other extracellular matrix components and inhibiting neocollagenesis.[5]

Advanced glycation end products (AGEs) are increasingly implicated in age-related diseases.[6] AGEs are free amino acids of nucleic acids, proteins, or lipids covalently bonded together under high-glucose conditions.[7] Accumulating in the skin throughout aging and during high-glycemic states, AGEs lead to the transcription of proinflammatory genes through activation of the nuclear factor kappa B (NFkB), induce oxidative stress, and impair the biomechanical properties of skin through deleterious modification of collagen, elastin, and fibronectin.[6,8] Reducing the accumulation of AGEs and thus activation of the receptor for AGE (RAGE) through anti-hyperglycemic medications therefore may protect against skin aging. A summary of putative anti-aging mechanisms can be found in the Table.

Antihyperglycemic Medications and Skin Aging

Metformin

Metformin is a synthetic biguanide used as a first-line treatment for type 2 diabetes. By enhancing insulin sensitivity, decreasing glucose production in the liver, increasing GLP-1, and reducing intestinal absorption of glucose, metformin effectively lowers basal and post-prandial blood glucose levels.[9,10] Metformin has been associated with a reduction in early mortality due to age-related diseases and this effect is theorized to be a result of its antihyperglycemic actions.[2] Studies specifically investigating the impact of metformin on skin aging have been conducted in vitro and using animal models. Treatment of human foreskin fibroblasts with 100 μM metformin attenuated photoaging

Table 1. Putative Anti-Skin Aging Mechanisms of Antihyperglycemic Drugs

Drug	Anti-aging Mechanisms
Metformin	Decreased activation of RAGE/NFkB pathway[22] Decreased ROS accumulation[11] Reduced mitochondrial autophagy (mitophagy)[11] Inhibits activation of PI3K/AKT/mTOR signaling pathways[11] Reduced photoaging by UVA and UVB radiation[11,12] Decreased collagen degradation[13,14] Reduced MMP expression[11] Decreased fibroblast apoptosis[13,14]
GLP-1 Receptor Agonists	Reduces expression of inflammatory factors IL-17, IL-22, IL-23, and TNF alpha[17] Reduces influx of invariant natural killer T cells[16] Reduces C-reactive proteins[19] Reduces MMP-9 and MMP-9/TIMP ratios[19] Induces oxidative defense genes HO-1 and NQO1[20] Inhibits NAD(P)H oxidases[21]
Both	Decreased AGEs[22,23]

Abbreviations: interleukin (IL), tumor necrosis factor (TNF), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinases (TIMP), heme oxygenase 1 (HO-1), quinone oxidoreductase 1 (NQO1), nicotinamide adenine dinucleotide phosphate (NADPH), advanced glycation end products (AGEs), receptor of advances glycation end products (RAGE), reactive oxygen species (ROS), phosphatidylinositol 3-kinases (PI3K), mammalian target of rapamycin (mTOR)

due to UVA irradiation through reduced ROS accumulation and mitophagy, and the attenuation of the DNA-repairing phosphatidylinositol 3-kinases (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways[11]; in vivo, UVA-irradiated mice treated with 10 mg/kg/day of metformin showed decreased signs of skin photoaging grossly and histologically and had significantly decreased expression of MMP1 and the mitophagy protein Parkin.[11] Similarly, signs of UVB-induced photoaging were attenuated following the topical application of 0.6% metformin cream to mice skin.[12] Furthermore, in vitro studies exploring the effects of 50 μM and 500 μM metformin on the viability of fibroblasts under high-glucose conditions (50 μM) found both doses of metformin significantly downregulated NFkB (p65) activity, inhibited apoptosis of fibroblasts, and increased production of collagen I-III compared to control.[13,14] Altogether, metformin appears to have protective properties against two major sources of skin aging, UVR-damage and AGEs.

Glucagon-Like Peptide-1 Receptor Agonists

Indicated for type 2 diabetes and weight management, GLP-1 RAs increase incretin hormones and glucose-dependent insulin release, decrease glucagon secretion, and reduce gastric emptying.[15] Given the similar antihyperglycemic effect of metformin, it is logical to suspect GLP-1 RAs may also have similar anti-aging effects. Indeed, multiple clinical trials demonstrated that GLP-1 RAs delay and treat age-related diseases, including osteoporosis, Parkinson's disease, atherosclerosis, kidney diseases, and non-alcoholic fatty liver disease.[3] GLP-1 RAs also ameliorate psoriasis by inhibiting generation of inflammatory cytokines.[16,17] Though GLP-1 RAs have not been studied within the context of skin aging, chronic inflammation is a known driver of skin aging as discussed above[18]; thus the anti-inflammatory benefits of GLP-1 RAs may curtail skin aging, namely through reduction of deleterious AGEs. Notably, GLP-1 RAs have demonstrated efficacy in diabetic rat wounds, significantly reducing C-reactive protein concentrations and MMP-9/tissue matrix metalloproteinase inhibitor-1 ratios in fibroblast cultures, reflecting increased expression of anti-inflammatory and pro-healing markers.[19] Purposeful studies on the effects of GLP-1 RAs and their impact on skin aging specifically are necessary to fully establish a relationship.

CONCLUSION

While the role of antihyperglycemic drugs such as metformin and GLP-1 RAs in combatting skin aging have yet to be fully described, dermatologists should be aware of the underlying mechanisms of these drugs and anticipate their potential inclusion in future armamentariums.

DISCLOSURE

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RESIDENT CORNER

- Each Friday, a new Pop Quiz question is posted to the Next Steps in Derm website, courtesy of Derm In-Review! Test your knowledge each week with these questions!
- Check out our series – Mnemonic Mondays! Next Steps in Derm features one Mnemonic from the Derm In-Review study guide.
- Plus, career development guidance and resources to support you as you navigate through residency.

PATIENT BUZZ SERIES

Do you ever field odd-ball patient questions and wonder where the information they presented came from? The monthly "Patent Buzz" series addresses recent dermatology news from the consumer press and provides background on the conditions and treatments your patients may ask about at their next office visit.

THERAPEUTIC CHEAT SHEET SERIES

Our therapeutic cheat series gives you a quick reference guide on the use of new or complex therapies.

JDD CORNER

Editorial highlights each month from the *Journal of Drugs in Dermatology (JDD)*. PLUS, take an in-depth look at the best and most unique case reports from the *Journal of Drugs in Dermatology (JDD)*.

VIDEO CONTENT

Next Steps in Derm has a robust library of video pearls, webinars, and virtual conferences. With new content being added regularly!

CONFERENCE COVERAGE

Stay up to date on the latest medical, aesthetic, and surgical dermatology topics presented at MedscapeLive!/SanovaWorks conferences including ODAC, Skin of Color Update, Pigmentary Disorders Exchange Symposium, and more!

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CME/CE

PIGMENTARY DISORDERS EXCHANGE SYMPOSIUM

JUNE 7–8, 2024

LOEWS CHICAGO HOTEL | CHICAGO, ILLINOIS

IN-PERSON

After an extremely successful inaugural event, the 2nd Annual Pigmentary Disorders Exchange Symposium will bring back together world-renowned dermatology experts who will spend two full days diving deep into pigmentary disorders in the full spectrum of skin tones, from lightest through darkest.

Pigmentary Disorders Exchange Symposium will allow participants to increase their understanding of:

» The effects of pigmentary disorders on patients' quality of life.

» The need for paradigm shifts in how we approach these individuals.

» The pathogenesis, nuances in clinical presentation, and full range of therapeutic options, including topical approaches, oral interventions, and procedural modalities, for the full spectrum of diseases from hyperpigmentation to hypopigmentation.

Each session will include patient cases, thought-provoking discussions, and plenty of interactive Q&A time so that you may bring your most pressing questions to our faculty.

From lightest to darkest, pigmentary disorders affect the full spectrum of skin tones. Join us to learn more!

RECEIVE 30% OFF REGISTRATION!

USE CODE **PDE30**

Register today at **pigmentarydisorders.com**

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