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SPECIAL FOCUS: LASERS, LIGHT SOURCES, AND DEVICES

Décolleté Rejuvenation

Skin Laxity and Dimpling

Wound Healing After Laser Skin Resurfacing

Sequential Treatment of AK and Photoaging

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ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

For adults with plaque psoriasis

workingtogether

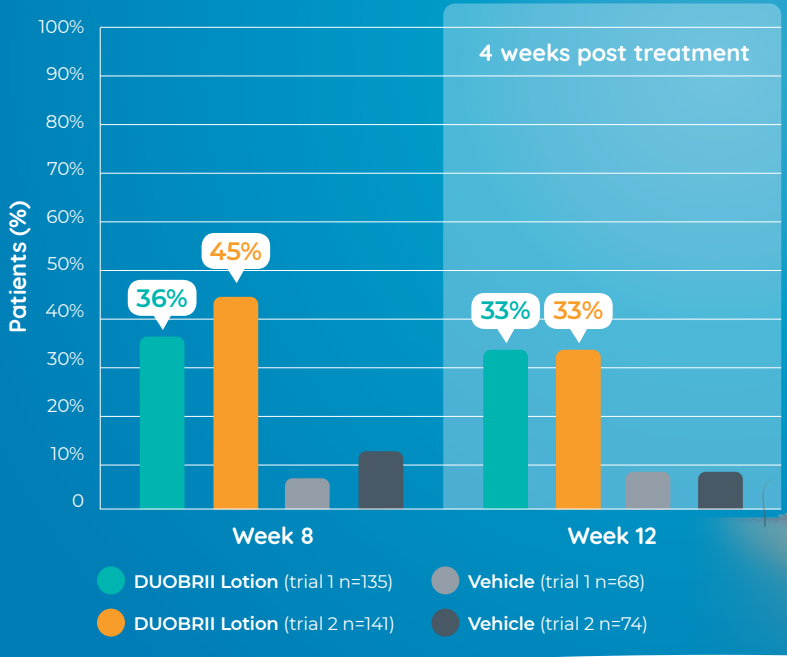
DUOBRII® (halobetasol propionate and tazarotene) Lotion 0.01% / 0.045%

DUOBRII Lotion is the only steroid/retinoid topical therapy. The AAD confirms that the combination of a steroid and a retinoid, such as **halobetasol** and **tazarotene**, may delay the relapse of plaque psoriasis and extend treatment duration.[1-3]

DUOBRII Lotion demonstrated extended remission 4 weeks post treatment[1]

2 phase 3 trials

Patients who achieved treatment success* with QD dosing (8 week primary endpoint)[1,4]



The only potent-to-superpotent steroid that has no time limits on use; use only until control is achieved.[1,5-9]

DUOBRII Lotion was studied in two 8-week clinical trials and a 1-year safety study. Discontinue treatment if atrophy, striae, telangiectasias, or folliculitis occurs.[1,10]

Indication

DUOBRII® (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, is indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Contraindication

DUOBRII Lotion is contraindicated in pregnancy.

Warnings and Precautions

- Women of child-bearing potential should be warned of the potential risk of fetal harm from DUOBRII and use adequate birth-control. A negative result for pregnancy should be obtained within 2 weeks prior to treatment. If the patient becomes pregnant during treatment, discontinue DUOBRII Lotion and advise patient of the potential hazard to the fetus.
- DUOBRII Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during or after treatment and may require that patients be evaluated periodically during treatment.
- Predisposing factors for HPA axis suppression include: use of more potent corticosteroids, use on large areas, use under occlusive dressings, use on altered skin barrier, concomitant use of other steroids, liver failure and young age.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. If these effects occur, discontinue until the integrity of the skin has been restored. Do not resume treatment if contact dermatitis is identified. DUOBRII Lotion should not be used on eczematous skin, as it may cause severe irritation.
- Avoid exposure to sunlight, sunlamps and weather extremes. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers because of the increased potential for photosensitivity.
- Topical corticosteroids may increase the risk of cataracts and glaucoma; advise patients to report any visual symptoms and refer to an ophthalmologist if needed.

Adverse Events

- The most common adverse events in clinical trials were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

To report SUSPECTED ADVERSE REACTIONS, contact Ortho Dermatologics at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

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

AAD = American Academy of Dermatology
QD = once daily

*Treatment success was defined as at least a 2-grade improvement from baseline in Investigator's Global Assessment (IGA) score, and a score of "clear" or "almost clear" (primary endpoint at week 8).[1]

Study design: DUOBRII Lotion was assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 418 adult patients with psoriasis. Patients were treated with DUOBRII Lotion or vehicle, applied once daily and evaluated at 2, 4, 6, 8 weeks (primary endpoint), and post treatment at 12 weeks.[1]

References: 1. DUOBRII Lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC. **2.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed February 12, 2020. **3.** Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 2009;60(4):643-659. **4.** Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: results of two phase 3 randomized controlled trials. *J Am Acad Dermatol*. 2018;79(2):287-293. **5.** Clobetasol propionate cream [prescribing information]. Lincolnton, NC: Cosette Pharmaceuticals, Inc. **6.** Diprolene lotion [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp. **7.** Enstilar foam [prescribing information]. Madison, NJ: LEO Pharma Inc. **8.** Halobetasol propionate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **9.** Mometasone furoate cream [prescribing information]. South Plainfield, NJ: G&W Laboratories, Inc. **10.** Data on file.

Help your patients save at **DUOBRII.com**

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe DUOBRII safely and effectively. See full Prescribing Information for DUOBRII.

DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% for topical use

INDICATIONS AND USAGE

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

Pregnancy

DUOBRII Lotion is contraindicated in pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Risk

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Tazarotene is teratogenic, and it is not known what level of exposure is required for teratogenicity in humans *[see Contraindications and Clinical Pharmacology]*. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits *[see Use in Specific Populations]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to DUOBRII Lotion therapy. Initiate DUOBRII Lotion therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion therapy *[see Use in Specific Populations]*.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects

DUOBRII Lotion contains halobetasol propionate, a corticosteroid, and has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with DUOBRII Lotion was evaluated in a study of 20 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area. The subjects were treated once daily for 8 weeks and assessed for HPA axis suppression at Weeks 4 and 8. HPA axis suppression occurred in 3 out of 20 (15%) subjects at Week 4 and none (0%) of these 20 subjects had HPA axis suppression at Week 8 *[see Clinical Pharmacology in full Prescribing Information]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including DUOBRII Lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug or reduce the frequency of application. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids because of their larger surface-to-body mass ratio *[see Use in Specific Populations]*.

Local Adverse Reactions

Local adverse reactions may include atrophy, striae, telangiectasias, folliculitis and contact dermatitis. Some local adverse reactions may be irreversible. If these adverse reactions occur, discontinue the medication at least until the integrity of the skin is restored; do not resume treatment if allergic contact dermatitis is identified.

Avoid use of DUOBRII Lotion on eczematous skin, as it may cause severe irritation.

Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of DUOBRII Lotion. Patients must be instructed to use sunscreens and protective clothing when using DUOBRII Lotion. Patients with sunburn should be advised not to use DUOBRII Lotion until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using DUOBRII Lotion.

DUOBRII Lotion should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Ophthalmic Adverse Reactions

Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of DUOBRII Lotion until the infection has been adequately treated.

ADVERSE REACTIONS

Clinical Trials Experience

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

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 410 adults with plaque psoriasis were treated with DUOBRII Lotion or vehicle lotion and had post-baseline safety data. Subjects applied DUOBRII Lotion or vehicle lotion once daily for up to eight weeks. The adverse reactions occurring in ≥1% of the subjects treated with DUOBRII through Week 8 were contact dermatitis (7%), application site pain (3%), folliculitis (2%), skin atrophy (2%), and excoriation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, DUOBRII Lotion may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from DUOBRII Lotion during pregnancy; therefore, DUOBRII Lotion should be discontinued as soon as pregnancy is recognized *[see Contraindications, Warnings and Precautions, Clinical Pharmacology]*.

Observational studies suggest an increased risk of low birthweight in infants with the maternal use of potent or very potent topical corticosteroids *(see Data)*.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose 11 times the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 116 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 9 and 228 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 9 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during the period of organogenesis to pregnant rats and rabbits *(see Data)*. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of DUOBRII Lotion.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (11 times the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5%, 0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (116 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; malformations and post-implantation loss were observed in rats and rabbits at doses producing 9 and 228 times, respectively, the MRHD (based on AUC comparisons).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (16 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to 5 times the MRHD (based on AUC comparison).

Lactation

Risk Summary

There are no data on the presence of tazarotene, halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with DUOBRII Lotion.

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUOBRII Lotion and any potential adverse effects on the breastfed child from DUOBRII Lotion.

Clinical Considerations

Advise breastfeeding women not to apply DUOBRII Lotion directly to the nipple and areola to avoid direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing

DUOBRII Lotion is contraindicated in women who are pregnant. Females of reproductive potential should be warned of the potential risk and use adequate birth-control measures during treatment with DUOBRII Lotion. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior to DUOBRII Lotion therapy, which should begin during menstruation.

Contraception

Based on animal studies, DUOBRII Lotion may cause fetal harm when administered to a pregnant female *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment with DUOBRII Lotion.

Pediatric Use

Safety and effectiveness of DUOBRII Lotion in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children *[see Warnings and Precautions]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema *[see Warnings and Precautions]*.

Geriatric Use

Of the 270 subjects exposed to DUOBRII Lotion in clinical trials, 39 subjects were 65 years or older. Clinical trials of DUOBRII Lotion did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposure at the highest dose was 35 times the MRHD (based on AUC comparison).

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day, approximately 0.53 times the MRHD based on BSA comparisons, indicated no impairment of fertility or general reproductive performance.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was 5 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 17 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 30 times the MRHD (based on AUC comparison).

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Bausch Health Americas, Inc.
Bridgewater, NJ 08807 USA

By:
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DRUGS • DEVICES • METHODS

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GUEST EDITORIAL

1024 **Fractional CO_2 Laser Treatment for Vulval Skin and Objective Quantifiable Effect on Vaginal pH**
Macrene Alexiades MD PhD

ORIGINAL ARTICLES

1026 **Clinical Trial Evaluating the Long-Term Efficacy of Microfocused Ultrasound With Visualization for Décolleté Rejuvenation**
Sabrina G. Fabi MD, Monica Boen MD, Marwan Alhaddad MD, Mitchel P. Goldman MD

1030 **The Influence of Different Treatment Combinations on Skin Laxity and Dimpling**
Rolf Bartsch MD, Gabriela Casabona MD, Christian Sitzwohl MD, Oliver Kimberger MD, Jeremy B. Green MD, Julia Stanger MD, Konstantin Frank MD, Emy C. Onishi MD, Sebastian Cotofana MD PhD

1040 **Prevention of Scarring With Intraoperative Erbium:YAG Laser Treatment**
Hiren Kolli BS, Ronald L. Moy MD

1044 **Red Deer Umbilical Cord-Derived Stem Cell Conditioned Media Combined With Ablative Resurfacing of the Face**
Elika Hoss MD, Ramya Kollipara MD, Marwan Alhaddad MD, Monica Boen MD, Mitchel P. Goldman MD

1050 **Wound Healing Treatments After Ablative Laser Skin Resurfacing: A Review**
Hayley Leight-Dunn MD, Margot Chima MD, Elika Hoss MD

1056 **Grover Disease Associated With Chemotherapy: Review of Potential Patho-physiology, Current Treatments, and Future Directions**
Jacob Beer BA, Misha Rosenbach MD

1065 **Sequential Treatment of Actinic Keratosis and Photoaging by Daylight PDT and Injectable NASHA Gel as Skin Booster**
Magda Belmontesi MD

ORIGINAL ARTICLES (CONTD)

1069 **Choosing the Right Partner: Complementing Prescription Acne Medication With Over-the-Counter Cleansers and Moisturizers**
Edward Lain MD FAAD, Anneke E. Andriessen PhD

1076 **At-Home Transvaginal Device Following Fractional Carbon Dioxide Laser Treatment for Genitourinary Syndrome of Menopause**
Macrene Alexiades MD PhD

1080 **Variables Affecting Delivery of Glycopyrronium Tosylate Through Human Skin In Vitro**
Franceso Caserta, Jon Lenn PhD, Hans Hofland PhD

1086 **Effects of Tazarotene 0.045% Lotion on Quality of Life in Patients With Moderate-to-Severe Acne**
Leon H. Kircik MD, Edward Lain MD MBA, Michael Gold MD, Bruce Katz MD, Hilary Baldwin MD, Eric Guenin PharmD, PhD MPH, Anya Loncaric MS, Radhakrishnan Pillai PhD

1093 **Tirbanibulin Ointment 1% as a Novel Treatment for Actinic Keratosis: Phase 1 and 2 Results**
Steven Kempers MD, Janet DuBois MD, Seth Forman MD, Amy Poon BS MA, Eva Cutler BS BA, Hui Wang PhD, David L. Cutler MD FRCP(C), Jane Fang MD, Rudolf Kwan MBBS MRCP

1101 **Therapies for Psoriasis: Clinical and Economic Comparisons**
Albert Marchetti MD, Tina Bhutani MD, Benjamin Lockshin MD, Daniel M. Siegel MD, Frederick Behringer MD

CASE REPORTS

1110 **Rapid Evolution of a Squamous Cell Carcinoma In Situ to Locally Invasive With Perineural Involvement**
Margit Juhasz MD MSc, Joel L. Cohen MD

1112 **Ablative Fractional Resurfacing for Chronic Wounds from Traumatic Scarring: A Case Report and Literature Review**
Joseph N. Mehrabi, Kristen M. Kelly MD

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LETTERS TO THE EDITOR

1117 **The Association of Professors of Dermatology Program Directors Task Force and Residency Program Transparency Work Group Guidelines on Residency Program Transparency**
David Rosmarin MD, Adam J. Friedman MD, Nicole M. Burkemper MD, Kristin M. Nord MD, Andrea T. Murina MD, Jennifer T. Huang MD

1119 **Geographic Variations in Biologic Therapy and Disease Characteristics: A Pilot-Study in the Corrona Psoriasis Registry**
Clinton W. Enos MD, Katie A. O'Connell MS, Ryan W. Harrison MS, Robert R. McLean DSc MPH, Blessing Dube MPH, Abby S. Van Voorhees MD

1123 **Remission of Refractory PASH Syndrome Using Ixekizumab and Doxycycline**
Muhammad I. Gul BS, Vivek Singam BLA, Cody Hanson MD, Brett C. Neill MD, Daniel J. Aires MD JD, Anand N. Rajpara MD

BRIEF COMMUNICATIONS

1125 **The Potential for Teledermatology in Managing and Diagnosing Patients With Cutaneous Lymphomas**
Jacob Beer, Edward Hadeler, Keyvan Nouri MD

1126 **Scleroderma in the Setting of Long-term Intermittent Phentermine Use**
Jacob Beer BA, Andrea Maderal MD

1127 **Revisiting Handwashing – As It Is Absolutely Essential**
Graham H. Litchman DO MS, Justin W. Marson MD, Neal Bhatia MD, Brian Berman MD PhD

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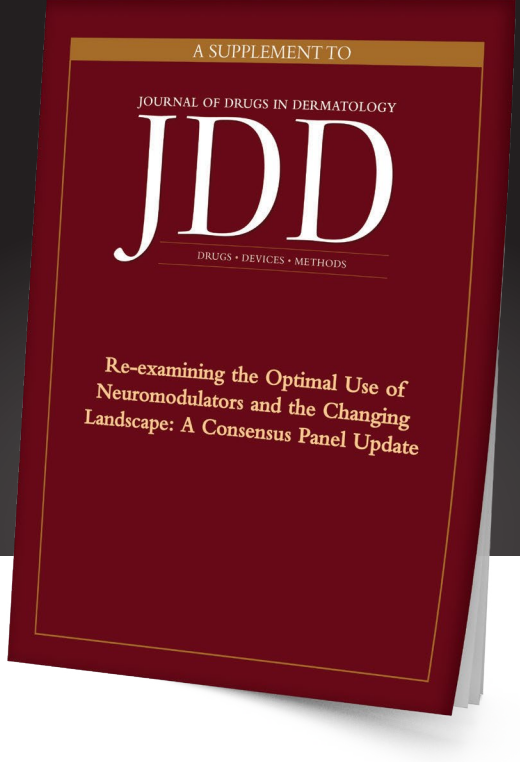

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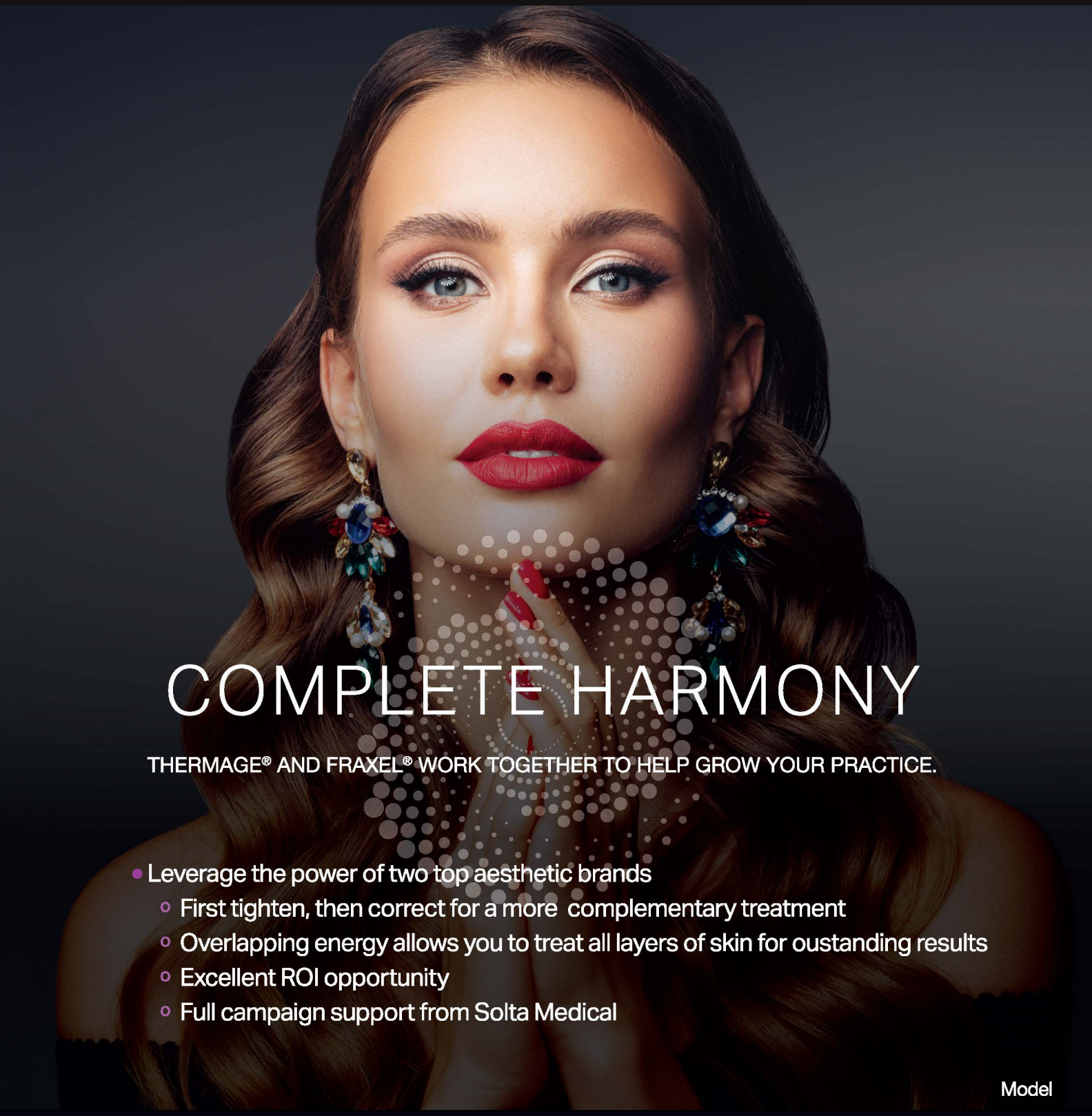

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GUEST EDITORIAL

Journal of Drugs in Dermatology

Fractional CO_2 Laser Treatment for Vulval Skin and Objective Quantifiable Effect on Vaginal pH

Macrene Alexiades MD PhD

Yale University School of Medicine, New Haven, CT; Dermatology & Laser Surgery Center of New York, New York, NY

Macrene Alexiades MD PhD

The expanding long-standing role of lasers in the treatment of genitourinary (GU) conditions is supported by the growing body of objective quantifiable data demonstrating time-sensitive improvements in vulvovaginal health.[1,2] Recently, a cohort analysis demonstrated that early intervention post-menopause restores normal vaginal health indices (VHI) with a statistically significant difference when administered <3 as opposed to >3 years post-menopause, indicating a critical window for restoring normalcy.[3] Given the time-urgency for the >50% of post-menopausal women who suffer from GU conditions, important facts include that the external genitalia are lined by skin, the long-standing history of lasers to treat mucosa, and that quantifiable reproducible measures of vaginal health have been tested alongside randomized controlled comparisons to the gold standard, attaining level I evidence-based data.

Lasers Treat Skin

The external genitalia–vulvae in women–are lined by skin, consisting of keratinized stratified squamous epithelium overlying the dermis connective tissue layer. Numerous lasers are approved for use for resurfacing of skin, including genital and perianal skin, therefore supporting the appropriateness of cutaneous laser application to the skin of this anatomic area.[4]

Lasers Treat Mucosa

The vagina is lined by non-keratinized stratified squamous epithelium, which pre-menopause is glycogen-rich, whereas post-menopause, it becomes atrophic with diminished glycogen; the underlying lamina propria is the connective tissue layer, which declines in vascularity, cellularity and ground substance with age. Fractional ablative laser treatment stimulates glycogen-rich epithelial thickening, and lamina propria cellularity and vascularity.[5,6] In addition to over 40 years of GU application in the treatment of genital warts, myomectomy, and surgery, lasers are also extensively used to treat the oral mucosa.[1,7]

Level I Evidence-Based Medicine

Fractional ablative lasers have been shown to be safe and efficacious compared to the gold standard of topical therapy in randomized controlled trials for the treatment of the genital skin, including lichen sclerosus and atrophic vulvovaginitis, constituting level I of clinical evidence.[8-10]

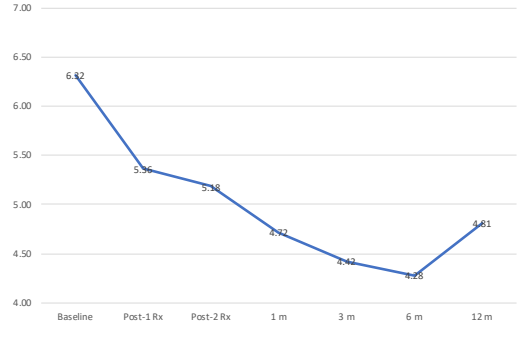
Alexiades Pathogenetic Theory

The metabolism of glycogen to lactic acid by the protective *Lactobacilli* bacteria creates the acidic environment (pH<4) in pre-menopausal vagina.[11] The inverse relationship between *Lactobacilli* populations and pH was shown by Athanasiou et al, underscoring its importance in GU syndrome of menopause (GSM).[12] In my theory, the loss of *Lactobacilli* due to diminishing glycogen levels in the face of post-menopausal hypoestrogenism results in the overgrowth of pathogenic microbes and yeast, leading to chronic vaginitis, *Candidiasis*, and lichen sclerosus in susceptible individuals. In the mid-2000s, Zerbinati and colleagues demonstrated that fractional CO_2 restores glycogen-rich vaginal epithelium, therefore providing the functional basis for restoration of the vaginal microbiome.[5,6]

Objective Scientific Measures

Vaginal pH provides an objective quantifiable endpoint at the pathogenetic crux of GSM. In the Alexiades clinical trial of fractional CO_2 vulvovaginal treatment (ClinicalTrials.gov Identifier: NCT02704741, CO2RE, Candela Lasers), mean post-menopausal vaginal pH was 6.32. Following three monthly fractional CO_2 laser treatments, acidic mean vaginal pH was restored to 4.28 at 6 months follow up (P<0.0001). pH levels began to slowly rise again between 6- and 12-months post-treatment, correlating with the recurrence of clinical symptoms.[3]

FIGURE: Mean Vaginal pH Post-Fractional CO_2 Laser Treatment. Vaginal pH was measured at baseline and following treatment with fractional CO_2 laser (CO2RE, Candela) to 12-month follow-up. ClinicalTrials.gov Identifier: NCT02704741.[3]



All timepoints statistically significant change from baseline, P<0.00001
Key: Rx=fractional CO2 laser treatment, m=months post-treatment follow-up

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Journal of Drugs in Dermatology

In sum, the extensive background of lasers to treat skin and mucosa, and the growing body of clinical data and objective scientific findings support the appropriateness of the fractional lasers for the treatment of GU conditions. More randomized controlled comparative trials to the gold standard employing objective quantitative measures will continue to elevate the level of scientific rigor to this important area of therapeutic advances for women's health.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Clinical Trial Evaluating the Long-Term Efficacy of Microfocused Ultrasound With Visualization for Décolleté Rejuvenation

Sabrina G. Fabi MD, Monica Boen MD, Marwan Alhaddad MD, Mitchel P. Goldman MD
Cosmetic Laser Dermatology, Goldman, Fitzpatrick, Butterwick, Groff, Fabi, Wu & Boen, San Diego, CA

ABSTRACT

Previous studies have demonstrated the beneficial effects of microfocused ultrasound with visualization (MFU-V) for treating chest wrinkles; however, those studies followed subjects for only 180 days. The objective of the following study was to assess the long-term effects of MFU-V for the treating chest wrinkles. Each subject was treated with 4-4.5 mm, 7-3.0 mm, and 10-1.5 mm transducers. Subjects were subsequently evaluated on post-treatment days 6, 12, 180, and 360. Digital images were obtained of the décolleté area of each subject prior to treatment and at each follow-up evaluation. Wrinkle severity was assessed using the validated Merz Décolletage Wrinkle Scales at each follow-up visit and Subject Satisfaction Questionnaires were completed on post-treatment days 180 and 360. Enrolled subjects (N=20) were female with a mean (SD) age of 54.9 (7.5) years (range, 44 to 71 years). The study was completed by 15 subjects. Subjects achieved a significant decrease in dynamic wrinkle scores over time (P<0.01). Baseline scores were significantly decreased at day 90 (P≤0.01) which remained significant at days 180 and 360 (for each, P<0.01). Subjects also showed significantly decreased at-rest wrinkle scores over time (P≤0.01). Baseline scores were significantly decreased at day 90 (P≤0.01), which remained significant at days 180 and 360 (for each, P=0.01). Mean (SD) subject satisfaction scores increased from 2.9 (1.8) on day 180 to 3.9 (1.8) on day 360.

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INTRODUCTION

Numerous treatments have been developed to treat skin laxity and photoaged skin, including energy-based technologies. The underlying basis for most of these energy-based therapies is to cause immediate collagen coagulation and contraction and stimulate fibroblast activity resulting in long-term neocollagenesis and neoelastogenesis.[1,2]

A device using microfocused ultrasound (MFU) creates multiple microthermal subcutaneous zones of coagulation of approximately 1 mm^3 at specific tissue depths while bypassing the epidermis, resulting in immediate collagen contraction and long-term neocollagenesis and tissue remodeling (Ulthera® System, Merz North America, Inc., Raleigh, NC). This device is designed to be used with an ultrasound imaging transducer (MFU-V) that enables visualization of tissue up to 8 mm below the surface of the skin (DeepSEE® Technology. Merz North America, Inc., Raleigh, NC). Tissue imaging enables the user to avoid non-target tissues such as bone and blood vessels. This non-invasive device is FDA-cleared to lift the eyebrow, improve lax submental and neck tissue, and lines and wrinkles on the décolletage.[3] Treatment with MFU-V is well-tolerated and provides improvements in skin laxity without altering epidermal barrier function.[4]

An initial pilot study assessed the use of MFU-V for treating skin laxity and rhytides on photodamaged areas on the décolletage.[5] Enrolled subjects demonstrated significant improvement in wrinkles and skin laxity at post-treatment days 90 and 180. Subject satisfaction was 100% at day 180. Based on these positive results, a larger prospective study further assessed the safety and effectiveness of MFU-V for improving lines and wrinkles of the décolleté.[6] A single MFU-V treatment provided significant aesthetic improvement for moderate-to-severe décolleté wrinkles for the 180-day duration of the study and possibly longer. Treating this area with MFU-V creates a smooth transition between the rejuvenated face, neck and chest.

Although the beneficial effects of MFU-V for treating the décolleté have been shown in numerous studies clinically, most were of only 6 month duration.[4-6] Only one MFU-V study demonstrated substantial lifting and tightening of facial and neck tissue with a high degree of patient satisfaction for up to 1 year.[7] The objective of this following study was to assess the long-term effects of MFU-V for the treatment of the décolleté, as patients commonly ask how long results from a single treatment will last.

METHODS

Participants

Study subjects were healthy adult women who were seeking improvement of wrinkles in the décolleté area. Eligible subjects were women 35 years of age or older with moderate to severe skin laxity of the chest that had a grade of 2 or greater on the Merz décolletage scale as assessed by the investigators.[8]

Exclusion criteria included a history of implanted electrical device of any kind; history or presence of any skin condition or disease in the planned treatment area that might interfere with the diagnosis or evaluation of study parameters (ie, atopic dermatitis, eczema, psoriasis); history or current evidence of a medical, psychological, or other disorder that, in the investigator's opinion, would preclude enrollment into the study; a subject planning any other cosmetic procedure to the study treatment area during the study period, other than the treatment that will be performed by the investigator; a subject who is pregnant, nursing, or planning a pregnancy during the study; and participation within 30 days prior to the start of the study in a drug or other investigational research study.

Interventions

Subjects entered the study during a 2-week screening period. MFU-V was administered on study day 1. Pre-medication for pain control was achieved with ibuprofen or acetaminophen 30 minutes prior to the procedure. Each subject was treated with 4 MHz-4.5 mm, 7 MHz-3.0 mm, and 10 MHz-1.5 mm transducers. Subjects were subsequently evaluated on post-treatment day 6, 12, 180, and 360. Digital images were obtained of the décolleté area of each subject prior to treatment and each follow-up evaluation. Subjects posed in At Rest, with arms at their sides, and Dynamic positions, with hands on opposite elbows. Wrinkle severity was assessed using the validated Merz Décolletage Wrinkle Scales[8] ranging from 0 (no wrinkles) to 4 (severe wrinkles). Subject Satisfaction Questionnaires were completed on post-treatment days 180 and 360 using scores ranging from 0 (completely dissatisfied) to 6 (completely satisfied).

Evaluations

Prior to treatment and at all subesequent visits, digital images were obtained of the treatment area (Vectra® 3D Imaging System; Canfield Scientific, Inc., Parsippany, NJ), which served as comparator images. Subjects were evaluated at week 6, day 90, day 180, and day 360 using the Merz dynamic and at rest Décolletage Wrinkle Scales.[8] A 7-point Subject Satisfaction Questionnaire was used to assess overall satisfaction on a scale from 0 (Completely Dissatisfied) to 6 (Completely Satisfied).

Overall improvement was assessed with single factor ANOVA. Two-sample t-test assuming equal variance was used to assess changes at individual time-points.

RESULTS

Study participants included 20 female subjects with a mean (SD) age of 54.8 (7.5) years (range, 44 to 71 years). Day 42 and 84 follow-up assessments included 18 subjects and day 180 and 360 assessments included 15 subjects.

The mean (SD) Merz Décolletage Wrinkle-Dynamic score decreased from 2.45 (0.37) at baseline to 1.89 (0.22) at week 12, 1.93 (0.21) at day 180, and 1.88 (0.12) at day 360. These changes represent a significant 23.3% decrease at week 12 ($P \leq 0.01$), which remained significant at day 180 ($P<0.01$) and day 360 ($P<0.01$) (Figure 1).

The mean Merz Décolletage Wrinkle–At Rest score decreased from 2.0 (0.11) at baseline to 1.56 (0.26) at week 12, 1.4 (0.83)

FIGURE 1. Changes in Merz Décolletage-Dynamic scores. Subjects showed a significant improvement at week 12 and days 180 and 360. *Denotes $P \leq 0.01$, **denotes $P<0.01$.

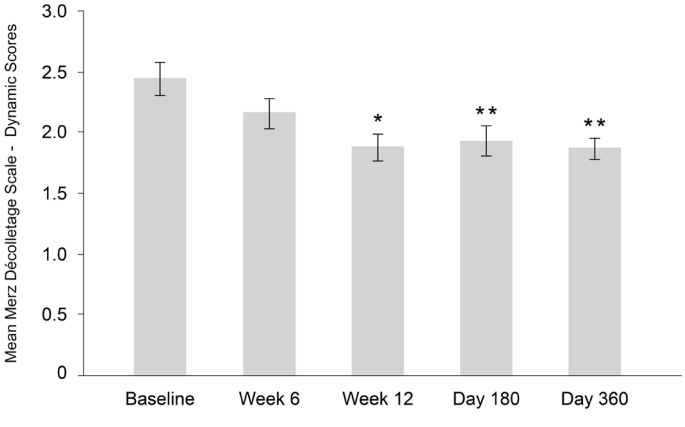
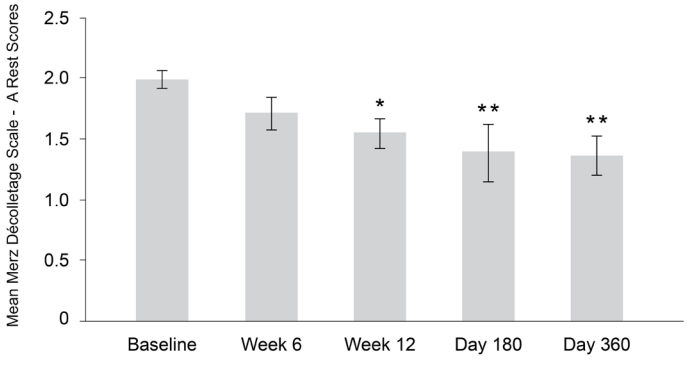


FIGURE 2. Changes in Merz Décolletage-At Rest scores. Subjects showed a significant improvement at week 12 and days 180 and 360. *Denotes $P \leq 0.01$, **denotes $P=0.01$.



at day 180, and 1.38 (0.38) at day 360. These changes represent a significant 22.5% decrease from baseline at week 12 ($P \leq 0.01$) and these differences remained significant at day 180 ($P=0.01$) and day 360 ($P=0.01$) (Figure 2).

At day 360, mean (SD) subject satisfaction scores had increased from 2.9 (1.8) on day 180 to 3.9 (1.8) on day 360 based on the 7-point scale (0–6), and included improvements in skin laxity, wrinkles, and overall skin quality. Improvements in baseline décolletage appearance are apparent at days 180 and 360 (Figure 3).

DISCUSSION

This is the first clinical trial to demonstrate the durability of MFU-V treatment in improving the appearance of the décolleté area by lifting and tightening the skin and reducing wrinkles for up to 360 days after a single session of treatment. Previous studies have demonstrated the effectiveness of MFU-V for the treatment of the décolleté area;[5,6] however, treated subjects were only followed up for 180 days. In our study, these improvements persisted for at least 1 year, but based on the apparent trend over time, improvement at rest may even continue even longer. Combining MFU-V with biostimulatory fillers have also shown improvements in chest wrinkling. The combination of MFU-V with poly-l-lactic acid has been shown to work synergistically for the rejuvenation of the face, neck, and décolletage.[9] Combining MFU-V with diluted calcium hydroxylapatite has also been shown to be effective for improving the appearance of lines and wrinkles on neck and décolletage for at least 90 days.[10]

While numerous other energy-based studies have shown to improve the appearance of the aging décolletage, none have shown this duration of improvement after a single session. Fractional radiofrequency microneedling has been shown to be effective for improving décolleté appearance following three treatments every 30 days; however, the final efficacy assessment was made on post-treatment day 30.[11] Another study reported on the use of high-intensity focused ultrasound and low-fluence Q-switched Nd:YAG laser in the treatment of the aging neck and décolletage but did not assess subjects after 16 weeks.[12] When a pulsed alexandrite laser with diffractive lens array was used for treating the photodamaged décolletage, significant improvements in dyspigmentation, keratosis, and skin texture were observed at 1- and 3-month follow-up assessments, but rhytides showed significant improvement only at the 1-month evaluation.[13] A comparative study assessing fractional laser and photodynamic therapy was only 12 weeks in duration.[14]; however, histological evidence post tissue heating indicated that neocollagenesis and dermal remodeling continues for more than 12 months. Moreover, postoperative edema after energy-based treatments could last for weeks to months, which may contribute to the initial improvement after any therapy. For these reasons, long-term durability studies are valuable in assessing the effectiveness of these treatment modalities.[15]

FIGURE 3. Décolletage appearance at baseline, day 180, and day 360 following treatment.

Limitations of this study include small sample size, some patients were lost to follow up, and there was lack of a control arm. Nonetheless, prospective long term studies evaluating the efficacy and safety of energy-based devices for skin rejuvenation are rare and our study adds valuable data to the literature show-casing the long-lasting effects of a single treatment with microfocused ultrasound.

CONCLUSION

Treatment of the décolleté with microfocused ultrasound with visualization significantly improves the dynamic and resting appearance of the aging décolleté. These improvements are durable and persist for a minimum of 1 year after a single treatment.

DISCLOSURES

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AUTHOR CORRESPONDENCE

Monica Boen MD
E-mail:..... mboen@clderm.com

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ORIGINAL ARTICLE

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The Influence of Different Treatment Combinations on Skin Laxity and Dimpling

Rolf Bartsch MD,[a,*] Gabriela Casabona MD,[b,*] Christian Sitzwohl MD,[a] Oliver Kimberger MD,[a] Jeremy B. Green MD,[c] Julia Stanger MD,[a] Konstantin Frank MD,[d] Emy C. Onishi MD,[e] Sebastian Cotofana MD PhD[f]

[a]Private Practice, Vienna, Austria
[b]Ocean Clinic, Marbella, Spain
[c]Skin Associates of South Florida, Coral Gables, FL
[d]Department for Hand, Plastic and Aesthetic Surgery, Ludwig – Maximilians University Munich, Germany
[e]Private Practice, Manila, Philippines
[f]Department of Clinical Anatomy, Mayo Clinic College of Medicine and Science, Rochester, MN

*Both authors contributed equally to this work

ABSTRACT

Objective: The aim of the study was to identify the effectiveness of the combination of tissue stabilized guided subcision, microfocused ultrasound, and minimally invasive calcium hydroxylapatite injections in various sequences for treating skin surface irregularities of the buttocks and thighs.

Material and Methods: 61 females (body mass index: 22.6 ± 2.4 kg/m², age: 37.2 ± 6.8 years) were enrolled in this randomized interventional prospective study. Treatment arms included a variable combination and sequence of three treatment modalities: (1) Tissue-stabilized guided subcision, (2) microfocused ultrasound, and (3) calcium hydroxylapatite injections. Six months after the final intervention skin laxity and skin dimpling severity scores were assessed by the study participants, the treating physicians and by eleven blinded independent board-certified experts.

Results: No adverse events were observed during the study that required intervention outside the standard of care treatment protocol. The combination of three treatment modalities was shown to provide greater improvement in skin laxity 1.88 (95% CI, 0.66–5.37) and skin dimpling 1.31 (95% CI, 0.61–2.81) scores as compared to any combination of two modalities. The combination of concomitant microfocused ultrasound and calcium hydroxylapatite injections followed three months later by tissue stabilized guided subcision yielded the greatest improvement in skin laxity 2.23 (95% CI, 0.51–9.82) and skin dimpling 1.79 (95% CI, 0.67–4.78) at 9-month follow-up.

Conclusion: This study provides evidence for the effectiveness of combination therapies for the improvement of skin surface irregularities on the buttocks and thighs.

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INTRODUCTION

Skin surface irregularities of the gluteal and posterior thigh regions can be majorly (though not exclusively) attributed to the effects of skin laxity and skin dimpling. This aesthetically unpleasing appearance can lead to profound feelings of body dissatisfaction, psychosocial stress, and decreased quality of life.[1–5]

A recent anatomic investigation by Rudolph et al[3] revealed that the subdermal junction is in a delicate balance between containment and extrusion forces. Containment forces are effected by skin thickness and the superficial fascial system whereas extrusion forces are generated by muscular contraction, high body mass index (BMI) and increased tissue pressure as observed in tissue edema.[3] A decrease in containment forces occurs with increasing age as the skin thins by 0.3% per year[3] and the superficial fascial system becomes less stable. The latter is a subdermally located biomechanical unit composed of the superficial fascia and the fibrous septae inserting superficially into the dermis, and extending deep to the deep fascia; thus, encompassing the superficial and the deep fatty subcutaneous layers.

Therapeutic options for the treatment of skin surface irregularities that have demonstrated efficacy include tissue-stabilized guided subcision (TSGS) which releases subdermal fibrous septae, and microfocused ultrasound (MFU) and calcium hydroxylapatite (CaHA) injections which induce neocollagenesis via fibroblast stimulation.[6–8] Whereas evidence exists for the effectiveness of each as monotherapy, there is no published data on the combination of the three treatment

TABLE 1.

Baseline Value for Age and BMI (mean ± standard deviation) for the Four Treatment Arms: Treatment Arm 1: TSGS (day = 0) followed by MFU (day = 90); Treatment Arm 2: TSGS (day = 0) followed by CaHA (day = 90); Treatment Arm 3: TSGS (day = 0) followed by MFU/CaHA (applied in the same session) (day = 90); Treatment Arm 4: MFU/CaHA (applied in the same session) (day = 0) followed by TSGS (day = 90)

	Treatment Arm 1	Treatment Arm 2	Treatment Arm 3	Treatment Arm 4
Age	38.5 ± 7.1	39.6 ± 6.2	35.1 ± 6.1	35.4 ± 6.9
BMI	24.2 ± 2.7	22.8 ± 1.9	22.0 ± 2.2	21.5 ± 1.9

modalities. It could be speculated that a combination of the treatments might have an additive effect resulting in better outcomes versus monotherapy or any combination of two modalities.

This randomized interventional prospective trial seeks to determine whether the combination of two or all three treatment modalities provides a better aesthetic outcome for skin surface irregularities, and which treatment sequence results in the greatest improvement in skin laxity and dimpling severity scores.

MATERIALS AND METHODS

Study Sample

The total study sample consisted of 61 females with an overall mean BMI at enrollment of 22.6 ± 2.4 kg/m^2 and a mean age of 37.2 ± 6.8 years (Table 1). Study participants were recruited amongst consecutive patients of the private practice of the first author (R.B.). The size of the total sample was selected to achieve a power of 80% with an alpha of 0.05.

Inclusion criteria were: female gender, negative pregnancy testing at enrollment, age between 22 and 55 years, BMI between 20.0 to 30.0 kg/m2, skin surface irregularities of the gluteal and posterior thigh region between 2 (moderate) and 3 (severe) when graded according to severity scales for both skin laxity and skin dimpling. Females were not included into the study if they had any type of surgical or non-surgical treatment of their gluteal or posterior thigh region, coagulation disorders, autoimmune diseases like lupus erythematosus, scleroderma, psoriasis or any type of dermatitis, or current use of any type of immunomodulatory medication including steroids or mycophenolate mofetil.

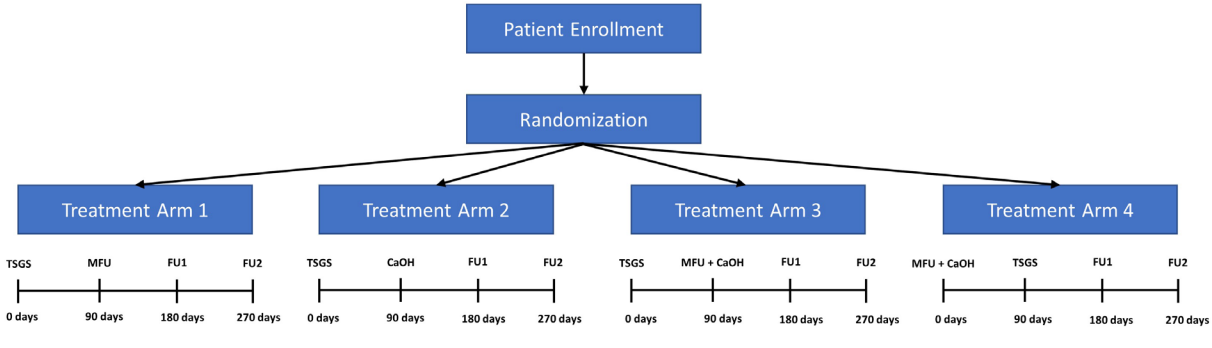
The study was approved by the local ethics committee of the Magistrat der Stadt Wien MA 15 (number: EK18-017-0618) and was conducted in accordance to Declaration of Helsinki[9] and the standards of good clinical practice. Study participants were briefed on the aims, scope and procedures of the study, and each participant provided written informed consent for the use of both their data and associated images prior to their initiation into the study.

Study Design

After obtaining written informed consent, participants were randomized into each of the four treatment arms following a random numbers table. Random numbers were enclosed in opaque sealed envelopes and distributed to participants at the beginning of the study (Figure 1). The gluteal and the posterior thigh regions of each participant were photographed according to a standardized protocol at baseline prior to the first intervention. The first intervention was conducted at baseline (day = 0) and the second intervention was conducted 90 days later (day = 90). A follow-up series of photographs of the gluteal and the posterior thigh region was obtained 180 days after the first and 90 days after the second intervention at day = 270.

Each treatment arm included a variation of the following treatment modalities:

FIGURE 1. Flow chart depicting the study design. After patient enrollment, patients were randomly assigned to the four treatment arms. TSGS = tissue stabilized guided subcision; MFU=Microfocused ultrasound; CaHA=Calcium Hydroxylapatite; FU1=Follow-up Appointment 1; FU2=Follow-up Appointment 2.



- TSGS (Cellfina®, Merz North America, Raleigh, NC
- MFU (Ultherapy®, Merz Pharma, Frankfurt/Main, Germany)
- Minimally invasive injections utilizing CaHA (Radiesse®, Merz Pharma, Frankfurt/Main, Germany)

Treatment Arms

Treatment Arm 1: TSGS (day = 0) followed by MFU (day = 90)
Treatment Arm 2: TSGS (day = 0) followed by CaHA (day = 90)
Treatment Arm 3: TSGS (day = 0) followed by MFU then CaHA (same session) (day = 90)
Treatment Arm 4: MFU then CaHA (same session) (day = 0) followed by TSGS (day = 90)

Outcome Assessment

Skin laxity and skin dimpling severity was graded on images according to validated severity scales with values ranging from 0 = no skin laxity/cellulite dimples, 1 = mild skin laxity/cellulite dimples, 2 = moderate skin laxity/cellulite dimples, 3 = severe skin laxity/cellulite dimples and 4 = very severe skin laxity/cellulite dimples.[10–12]

The grading was conducted at baseline (before any treatment; day = 0) and 180 days after the last treatment (= follow-up assessment at day = 270) on images by the study participants ("patients") and by the treating physicians R.B. and G.C. ("doctors"). Due to potential bias to the sequence of treatment or treatment arm, the baseline and the follow-up images were additionally scored by a panel of eleven blinded physicians (board-certififed plastic surgeons and dermatologists) with at least 5 years of experience in evaluating and treating skin surface irregularities (= termed "experts"). The experts' evaluation was conducted online via cloud-based image scoring with blinding to the sequence of treatment or treatment arm.

Subjective pain perception was recorded immediately after each treatment in each treatment arm according to a visual analogue scale (VAS) with values ranging from 0 (= no pain) to 10 (= pain as bad as you can imagine).

Treatment Modalities

Tissue-stabilized guided subcision (TSGS)

Prior to the procedure, dimples are marked with the patient standing upright. Next the patients are placed in the prone position and the buttocks and thighs are cleaned using a chlorhexidine-based solution and sterile draping is applied. After positioning the TSGS device over the marked dimple and capturing tissue with vacuum suction, 32.0 cc of local anaesthesia per site is infused containing 2 mg epinephrine and 1000 mg Lidocaine in 1000 cc 0.9% NaCL. Due to the vacuum capture during anesthesia administration, the pain of injection is minimal. After local anesthesia, the vacuum suction platform is used to capture tissue and then to guide a reciprocating microblade through preformed slots at a 6mm depth. The microblade precisely cuts the fibrous septae underlying each dimple. After all dimples are released dressings with gauze are applied. Expected effects of this therapy are erythema of the skin treated by the vacuum device and the formation of hematomas, which typically resolve in 7–14 days. To this point there are no reports of infection with the TSGS procedure.

Calcium hydroxylapatite (CHA)

CaHA is an injectable made of a degradable carboxymethylcellulose gel carrier surrounding particles of calcium hydroxylapatite. A 1.5 ml syringe of CaHA was mixed 1:1 with plain 2% lidocaine, and this 3.0 cc solution was into the one ipsilateral buttock/thigh using a 22G 50 mm blunt-tipped cannula in the subdermal plane through 3 points of entrance per side defined as follows:

I) One (patient) palm below the iliac crest in the middle of the buttock,
II) One (patient) palm above the femoral trochanteric depression at side of the buttock,
III) One (patient) palm below the gluteal crease.

The contralateral buttock and thigh were injected in the same fashion resulting in 6.0 cc total injected volume. Following injection, the CaHA was massaged to ensure even spread.

Micro-focused ultrasound (MFU)

MFU technology employs ultrasound waves applied externally to the skin and affecting the subdermally located superficial fascial system. The areas treated with MFU are the same as described for CaHA (see above). The MFU 4.5 mm transducer was placed onto the skin surface, and using a thin layer of ultrasound gel 25 treatment lines at the highest energy level (1.2 joules) were administered at each of the sites previously described for CaHA injection (areas I, II, and III) resulting in 75 treatment lines per patient side. Next, 75 treatment lines were delivered in the same fashion at the same sites with the 3.0 mm depth MFU transducer at its highest energy level (0.45 joules). Of note, when MFU and CaHA injections were performed concomitantly, MFU was performed first as the transducers are not able to be sterilized.

Statistical Analyses

Differences in the baseline and in the follow-up scores between the treatment arms were calculated using chi-square testing and between the three different score evaluators (patients / doctors / experts) using Kruskal-Wallis testing. Bivariate correlations were conducted between the number of dimples released and both the baseline and the follow-up scores. Paired analyses between the (ordinally scaled) baseline and follow-up scores were calculated using non-parametric paired sample analyses via the Wilcoxon test. Influences on the change in score between baseline and follow-up were calculated by running Poisson loglinear regression models with robust estimator and adjustment for

TABLE 2.

Baseline (day=0) and Follow-up (day=270) Scoring of Skin Laxity and Skin Dimpling Severity by the Female Study Participants (=Patient), by the Treating Physicians (= Doctors), and by the Independent Expert Panel. Values are presented per sample (count), median and interquartile range (IQR).

			Count	Median	IQR
Baseline	Skin dimpling severity	Patient	61	3	(2, 3)
		Doctors	61	2	(2, 3)
		Experts	61	2	(2, 3)
	Skin laxity severity	Patient	61	3	(2, 3)
		Doctors	61	2	(2, 3)
		Experts	61	2	(2, 3)
Follow-Up	Skin dimpling severity	Patient	61	2	(1, 2)
		Doctors	61	1	(1, 2)
		Experts	61	2	(1, 2)
	Skin laxity severity	Patient	61	2	(1, 2)
		Doctors	61	1	(1, 2)
		Experts	61	2	(1, 2)

age and BMI at the follow-up visit. Results are presented via the odds ratio and the accompanying 95% confidence interval (95% CI). All analyses were performed using SPSS Statistics 23 (IBM, Armonk, NY) and results were considered significant at a probability level of ≤ 0.05.

RESULTS

Baseline Assessment

Skin laxity and skin dimpling severity as scored by the patient, by the doctors and the by the blinded experts are presented in Table 2. Age, but not baseline BMI, was equally distributed across the treatment arms with P=0.165 and P=0.011. The distribution of the different skin laxity and skin dimpling grades (independent of the evaluator) did not differ statistically significantly between the four treatment arms with P=0.379 and P=0.586, respectively. There was a statistically significant difference in the assessment of skin dimpling severity between the three different evaluators with P=0.009 (mean ranks: patients = 102.05, doctors = 90.75, experts = 83.20), but not for skin laxity severity with P=0.118 (mean ranks: patients = 104.52, doctors = 94.32, experts = 77.16) (higher score indicates worse outcome).

Follow-up Assessment

No adverse events were observed during the study period that required medical intervention outside the standard of care treatment protocol. After the 9-months follow-up period (and 6-months after the last intervention), no statistically significant difference in the distribution of skin laxity and skin dimpling severity grades between the four treatment arms (independent of the evaluator) was observed with P=0.413 and P=0.675, respectively. A statistically significant difference in the scoring between the three evaluators was detected for both skin laxity and skin dimpling severity grades with P=0.003 and P=0.021, respectively. Mean ranks for skin laxity were: patients = 102.34, doctors = 74.12, experts = 99.54, whereas mean ranks for skin dimpling were: patients = 101.43, doctors = 77.53, experts = 97.03 (higher score indicates worse outcome).

Procedure Analyses

Pain Perception

Pain perception during the infiltration and the infusion steps of the TSGS procedure scored via the VAS were 3.10 ± 1.5 and 0.67 ± 0.7, respectively, and there was no statistically significant difference between the treatment arms with P=0.258. Pain perception during MFU was significantly increased in all treatment arms when compared to the treatment arm without MFU with 4.43 ± 2.3 vs 2.18 ± 1.6 with P=0.013.

Release of Dimples

The number of dimples released during the TSGS procedure correlated significantly with the skin dimpling severity score evaluated at the 9-month follow-up visit both for the doctors rp = 0.323, P=0.011 and the experts rp = 0.540, P<0.001, but not when scored by the patients rp = 0.228, P=0.078. Interestingly, the number of dimples released did not correlate at a statistically significant level with the change in the skin dimpling grades (follow-up grade minus baseline grade) for all three different evaluators: patients/doctors/experts: rp = 0.058, P=0.655 / rp = -0.090, P=0.491 / rp = -0.006, P=0.960.

Influence of Treatment Modality on Outcome Scores

Independent of the treatment arm, a highly statistically significant improvement in skin laxity (P<0.001) and skin dimpling (P<0.001) severity scores between baseline and the 9-months follow-up assessment was observed. This level of improvement (P<0.001) was assessed by the patients, the doctors and by the independent blinded observers when running paired unadjusted non-parametric analyses. (Figure 2, Figure 3, Figure 4, Figure 5)

FIGURE 2. Photograph showing the buttock and thigh of a patient before treatment according to treatment arm one (Treatment Arm 1: TSGS (day = 0) followed by MFU (day = 90) on the top and after treatment below.

FIGURE 3. Photograph showing the buttock and thigh of a patient before treatment according to treatment arm two (TSGS (day = 0) followed by CaHA (day = 90)) on the top and after treatment below.

FIGURE 4. Photograph showing the buttock and thigh of a patient before treatment according to treatment arm three (TSGS (day = 0) followed by MFU then CaHA (same session) (day = 90)) on the top and after treatment below.

FIGURE 5. Photograph showing the buttock and thigh of a patient before treatment according to treatment arm four (MFU then CaHA (same session) (day = 0) followed by TSGS (day = 90)) on the top and after treatment below.

Skin Laxity Severity Scale
(scored by the independent expert evaluators)

Calculating Poisson loglinear regression models with adjustment for age and baseline BMI and using treatment arm 1 (TSGS and MFU) as a reference, the odds of improving by at least one grade in the skin laxity severity score was 1.47 (95% CI, 0.23–9.25) for treatment arm 2 (TSGS and CHA), 2.21 (95% CI, 0.48 – 10.15) for treatment arm 3 (TSGS and MFU/CaHA) and 2.23 (95% CI, 0.51 – 9.82) for treatment arm 4 (MFU/CaHA and TSGS). (Figure 6)

Stratifying the treatment arms into two treatment modalities vs. three treatment modalities, Poisson loglinear regression models revealed a higher odds of improving by one or more grades in the skin laxity severity scale if all three modalities were employed with 1.88 (95% CI, 0.66–5.37) when compared to the application of two modalities; independent of sequence. (Figure 7)

Skin Dimpling Severity Scale
(scored by the independent expert evaluators)

Calculating Poisson loglinear regression models with adjustment for age and baseline BMI and using treatment arm 1 (TSGS and MFU) as a reference, the odds of improving by at least one grade in the skin dimpling severity score was 1.05 (95% CI, 0.27–4.07) for treatment arm 2 (TSGS and CaHA), 0.80 (95% CI, 0.21–3.00) for treatment arm 3 (TSGS, and MFU/CaHA) and 1.79 (95% CI, 0.67–4.78) for treatment arm 4 (MFU/CaHA and TSGS) (Figure 8).

FIGURE 6. Forest plots depicting the odds of improving by at least one grade in the skin laxity severity score and associated 95% confidence interval (CI) for each of the evaluators (expert, doctor, patient) and the respective treatment strategy compared to treatment arm A (TSGS + MFU) calculated with Poisson loglinear regression models.

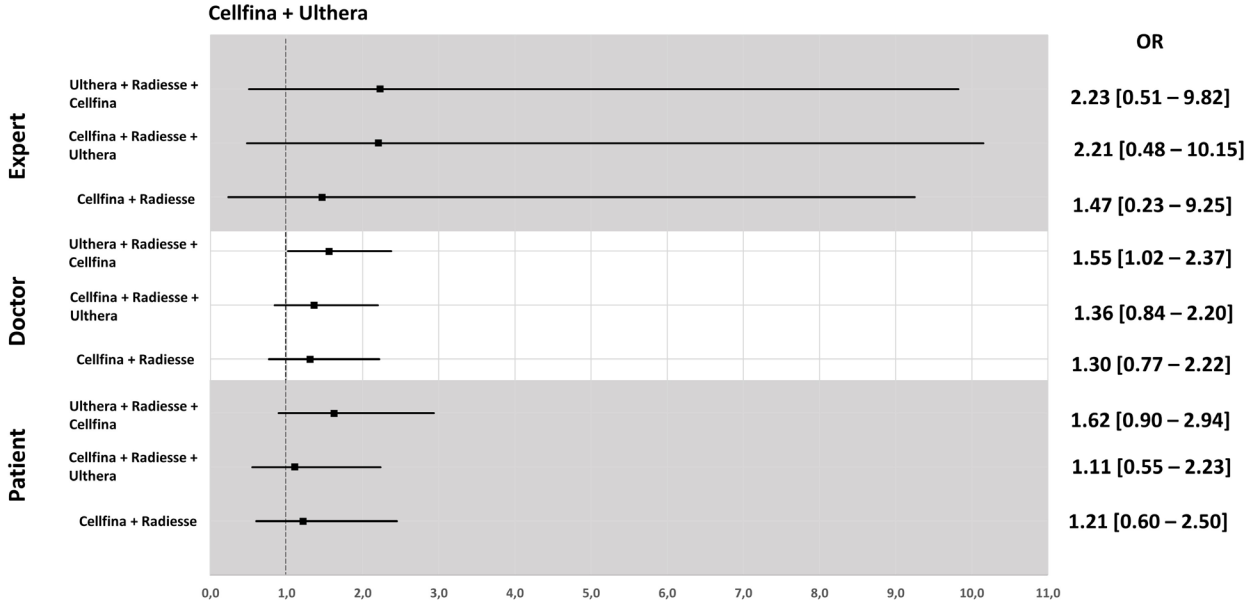


FIGURE 7. Forest plots depicting the odds of improving by one or more grades in the skin laxity severity scale and associated 95% confidence interval (CI) if all three modalities were applied when compared to the application of two modalities calculated with Poisson loglinear regression models.

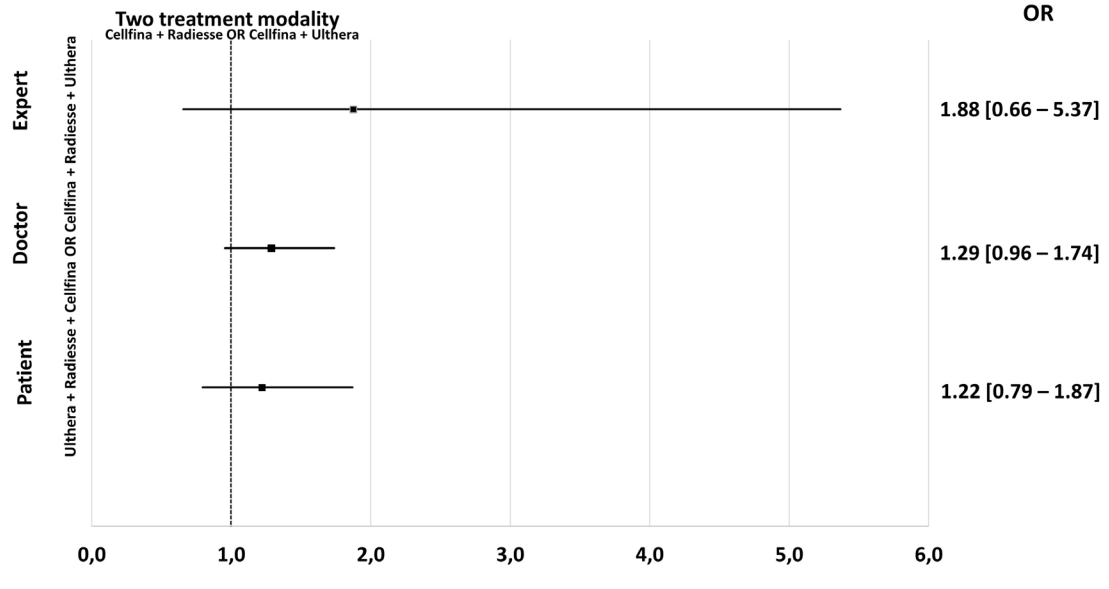


FIGURE 8. Forest plots depicting the odds of improving by at least one grade in the skin dimpling severity score and associated 95% confidence interval (CI) for each of the evaluators (expert, doctor, patient) and the respective treatment strategy compared to treatment arm A (TSGS + MFU) calculated with Poisson loglinear regression models.

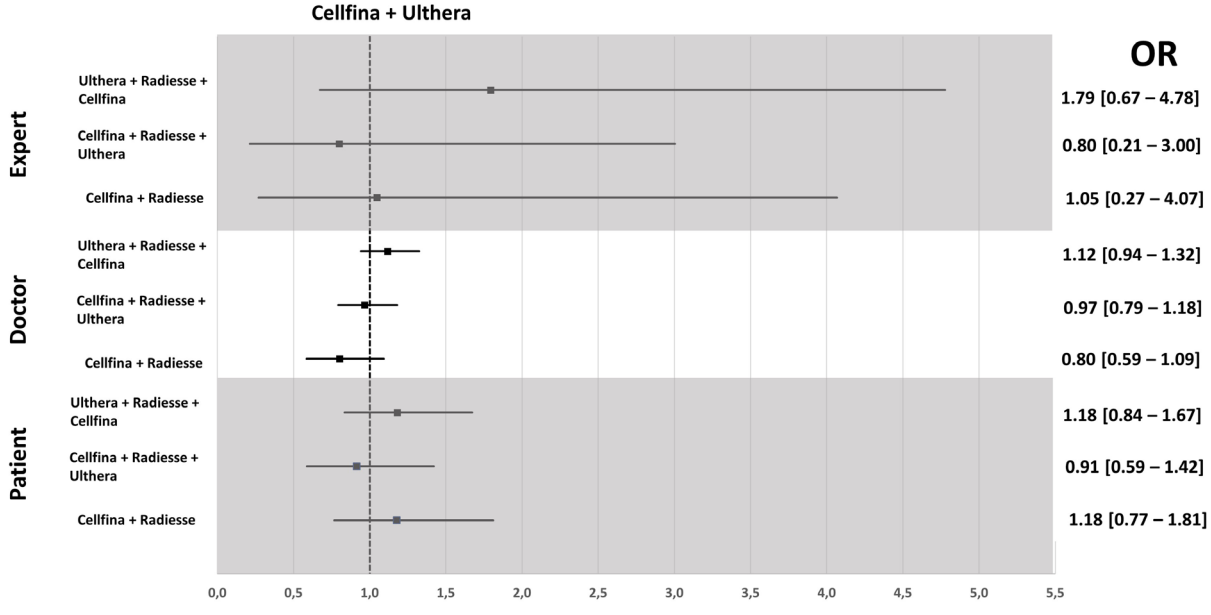
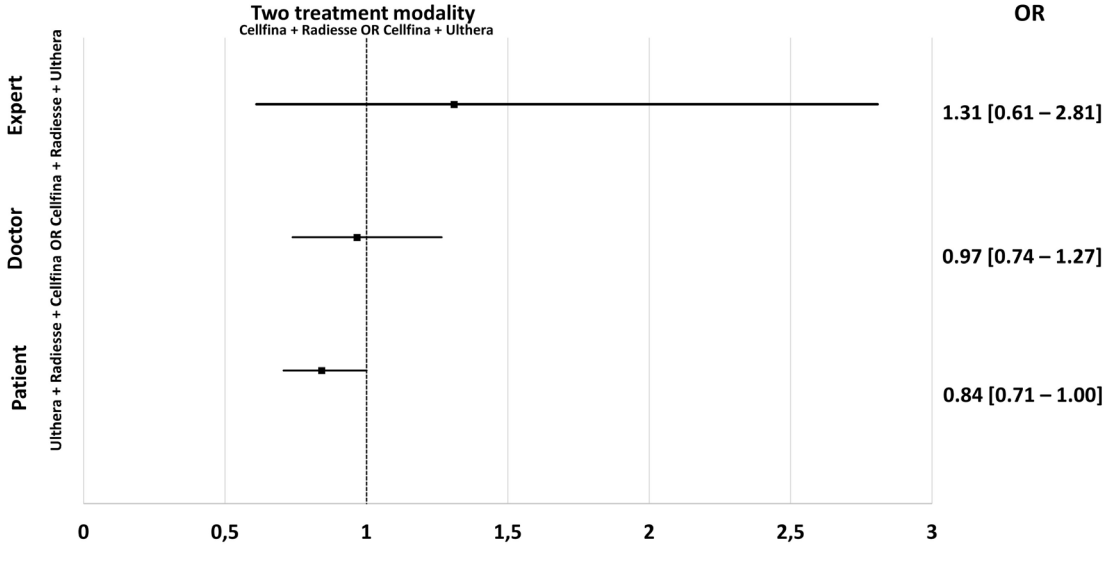


FIGURE 9. Forest plots depicting the odds of improving by one or more grades in the skin dimpling severity score and associated 95% confidence interval (CI) if three modalities were applied when compared to the application of two modalities calculated with Poisson loglinear regression models.



Stratifying the treatment arms into two modalities vs. three modalities, Poisson loglinear regression models revealed a higher odds of improving by one or more grades in the skin dimpling severity scale if all three modalities were utilized with 1.31 (95% CI, 0.61–2.81) when compared to the application of two modalities (Figure 9).

DISCUSSION

This prospective randomized interventional study enrolled 61 females and assigned them into four different treatment arms, with each of the arms having a different sequence and number of the following treatment modalities: (1) Tissue stabilized guided subcision (TSGS), (2) micro-focused ultrasound (MFU), (3) minimally invasive injections utilizing calcium hydroxylapatite (CaHA). The outcome of the study was based on the assessment of skin surface irregularities i.e. skin laxity and skin dimpling according to skin laxity and skin dimpling severity scales[11,12] 6 months after the last intervention. Skin laxity and skin dimpling severity scale assessment was performed by the study participants, by the treating physicians, and by eleven blinded independent board-certified aesthetic experts based on standardized images of the gluteal and posterior thigh regions.

The results revealed a highly statistically significant improvement in skin laxity (P<0.001) and skin dimpling (P<0.001) severity scores independent of the assigned treatment arm. The combination of three treatment modalities (independent of their sequence; treatment arm 3 and 4; despite not reaching statistical significance) had an increased odds of improving by at least one grade in skin laxity severity scale of 1.88 (95% CI, 0.66–5.37) and an increased odds of 1.31 (95% CI, 0.61–2.81) to improve by at least one grade in the skin dimpling severity scale when compared to the combination of two treatments modalities (independent of their sequence; treatment arm 1 and 2). When using treatment arm 1 (TSGS and MFU) as a reference, a gradual increase (despite not reaching statistical significance) in the odds of improving by at least one grade in skin laxity severity scale was observed with 1.47 (95% CI, 0.23–9.25) for treatment arm 2 (TSGS and CaHA), 2.21 (95% CI, 0.48–10.15), arm 3 (TSGS and MFU/CaHA) and 2.23 (95% CI, 0.51–9.82) for arm 4 (MFU/CaHA and TSGS). A similar gradual increase (despite not reaching statistical significance) was observed for improving by at least one grade in skin dimpling severity scale and when using treatment arm 1 (TSGS and MFU) as a reference: 0.80 (95% CI, 0.21–3.00) for treatment arm 3 (TSGS and MFU/CaHA), 1.05 (95% CI, 0.27–4.07) for treatment arm 2 (TSGS and CaHA), and 1.79 (95% CI, 0.67–4.78) for treatment arm 4 (MFU/CaHA and TSGS).

A strength of the present study is the controlled study design which utilized blinded randomization of the study participants into each of the four different treatment arms with an equal distribution of skin laxity and skin dimpling severity grades at baseline (P=0.379 and P=0.586, respectively). Another strength is the standardized treatment protocol for each of the four treatment modalities and the relatively large sample (n = 61) of female participants, which facilitated statistical analysis of the results. At the follow-up assessment (9 months after baseline, 6 months after the last intervention), a significant difference between the three evaluators was identified with the treating physicians scoring significantly better than the blinded experts and the treated patients for both skin laxity and skin dimpling scores (P=0.003 and P=0.021). This could be interpreted as an evaluator bias which could be regarded as a limitation of the study.

To potentially control for this bias, the assessment of the results by the eleven blinded expert evaluators was chosen as the primary outcome measure. Another limitation of the study is that no interim evaluation was performed. This could potentially have allowed for identification of specific effects for the different treatment modalities. However, as previous studies have shown that each treatment is effective as monotherapy,[4–6,8,13–17] the focus of this study was on the combination and the sequence of the utilized treatment modalities. An additional limitation of the study is the relatively young age of the cohort. Although it is consistent with the age group most commonly seen by the authors in clinical practice seeking buttock/thigh aesthetic improvement, it is unclear whether the results are generalizable to an older female population.

This study identified increased odds of improving by at least one grade in both skin laxity and skin dimpling severity scores if all three treatment modalities were utilized versus any two interventions, independent of their applied sequence. One potential explanation could be the occurrence of an additive effect of the treatment interventions affecting the subdermal interface with their unique modes of action. While TSGS releases subdermal fibrous connections and induces the formation of a horizontally (parallel to the skin surface) oriented neo-tissue plate (potentially scar tissue),[17] MFU leads to a tightening and shortening of the components of the superficial fascial system by the application of discrete TCP at 4.5 and 3.0 mm depth.[6] The minimally invasive injection of CaHA strengthens collagenous subdermal structures via its biostimulatory effect [6] and together with the other treatment modalities result in an overall reinforcing effect on the subcutaneous architecture. This synergistic strengthening could generate more stable balance between containment and extrusion forces an ultimately beget improved appearance of skin surface irregularities.

The most effective treatment combination (despite not reaching statistical significance) for the improvement of both skin laxity and skin dimpling scores was concomitant MFU/CaHA and followed three months later by TSGS. The underlying physiologic mechanisms leading to this superior outcome is subject to

speculation. This study did not include histologic or immune-histochemical analyses which could perhaps have provided additional insight into the observed outcomes. Future studies could expand upon the findings herein in a more experimental setting. A potential explanation could be that there is augmented benefit to stabilizing the roof (skin and subdermal interface) with MFU (4.5 mm and 3.0 mm) and CaHA injections prior to re-organization of the deeper located structural components (TSGS at 6.0 mm).

In contrast, TSGS followed 3 months later by MFU resulted in the lowest odds to improve the severity scales by at least one grade. Whether this effect was due to the fact that this treatment arm included only two treatment modalities (versus three modalities) or whether TSGS was farthest from the follow-up assessment, or whether it suggests the important missing contribution of CaHA injections in this treatment arm is remains elusive.

CONCLUSION

This prospective randomized interventional study provided evidence that the combination of TSGS, MFU, and CaHA injections is effective for the treatment of skin surface irregularities when assessed by skin laxity and skin dimpling severity scales. No adverse events were observed during the study period that required medical intervention outside the standard of care treatment protocol. The combination of three treatment modalities was shown to provide greater improvement in skin laxity and skin dimpling scores as compared to any of the two treatment modalities combined. The combination of MFU and minimally invasive injections of CaHA followed three months later by TSGS effected the greatest improvement at 9-months follow-up.

DISCLOSURES

R.B., G.C., and J.B.G. provide consulting and speaking services for Merz Pharmaceuticals GmbH & Co. KGaA. None of the other authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

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AUTHOR CORRESPONDENCE

Sebastian Cotofana MD PhD
E-mail:.....scotofana24@gmail.com

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Prevention of Scarring With Intraoperative Erbium:YAG Laser Treatment

Hiren Kolli BS,[a,b] Ronald L. Moy MD[b]

[a]Virginia Commonwealth University School of Medicine, Richmond, VA

[b]Research Department, Moy-Fincher-Chipps Facial Plastics/Dermatology, Beverly Hills, CA

ABSTRACT

Background: Scars can develop as a result of surgical incisions and pose psychological, cosmetic, and physical stress to the patients affected. Lasers have been used for scar revision, but little information exists regarding intraoperative use and efficacy.

Objective: To evaluate a 2,940-nm fractional erbium:YAG laser to improve scar appearance when used immediately after skin closure.

Methods and Materials: Patients undergoing complex closures of at least 1.5 cm in length were recruited. Half of the wound received treatment with 2,940 erbium:YAG laser immediately after skin closure. Follow up occurred at 1 week and 12 weeks, postoperatively. Patient self-assessment was performed at the final visit. Photographs were evaluated by three blinded dermatologic surgeons.

Results: 18 patients completed the treatment protocol and follow-up. 61.1% of patients reported that the treated side was cosmetically superior to the control side. A majority of patients said the treated side was superior in elevation, erythema, and similarity to normal skin. Physician evaluation showed that the treated half was cosmetically superior in 12 of 18 patients (66.7%).

Conclusions: This study demonstrates that a 2,940-nm erbium:YAG laser treatment, performed immediately after surgery, can improve the appearance of a surgical scar.

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INTRODUCTION

Scarring is an inevitable consequence of surgical incision. While physicians strive to employ excellent surgical technique, the outcome of a surgical scar is often unpredictable. There are a number of therapeutic strategies used for the reduction and prevention of scars. Nonsurgical options include corticosteroids, fluorouracil, and pressure therapy while more aggressive options include various surgical techniques and dermabrasion. In particular, laser technology has become the treatment of choice for many types of scars and has shown both clinical and cosmetic benefits for the patient.[1]

Though the initial scar after surgery can be expected to change over time, a 6 to12-month delay before revision is recommended, with a 2-month delay for more unfavorable scars.[2] However, recent studies have emphasized the importance of early laser resurfacing to minimize scar formation. Capon et al evaluated the immediate post-surgical wound closure use of an 810-nm diode laser treatment.[3] At 12 months, the treated portion scored significantly better compared with controls. Ozog and Moy reported that 1–2 passes of a fractional carbon dioxide laser to half of a surgical wound immediately following subcutaneous sutures significantly improved the appearance and texture of scars.[4] In 2018, Du et al observed an apparent aesthetic scar improvement in Asian patients treated with intraoperative fractional CO2, but did not have controls for comparison.[5] In 2002, Rohrer and Ugent conducted a study on 10 patients with use of a short-pulsed erbium:YAG laser intraoperatively.[6] Though there was no significant difference, there was a better overall aesthetic appearance of the side of the scar that had been resurfaced.

Our study aims to quantify the improvement resulting from fractional erbium:YAG laser treatment. To our knowledge, no report on fractional erbium:YAG laser intervention on the same day of skin suture has been published thus far.

MATERIALS AND METHODS

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Patients undergoing a complex linear closure of at least 1.5 cm in length after excisional surgery were asked to voluntarily participate in the trial and were enrolled after written informed consent was obtained. To be enrolled, the patients had to be 18 years of age or older with a wound length of 1.5 cm or greater, willing to comply with the protocol of standard postoperative care and be able to attend the postoperative visits. Patients on systemic immunosuppressants or with a dermatologic disease in the target site that may interfere with examination were excluded from the study.

After standard undermining and hemostasis, subcuticular 4-0 buried sutures were placed (Vicryl; Ethicon Inc, Somerville, NJ) along the entire length of the wound. The entire wound was then closed with a running epidermal suture of either 5-0 fast-absorbing gut sutures (Ethicon Inc.) when the wound was on the face, or 4-0 Prolene (Ethicon Inc.) for the trunk and extremities. All attempts were made to ensure the wound edges were evenly approximated over the entire length and slightly everted. Immediate postoperative photographs were taken.

Each wound was measured, and the length divided in half. One half was randomly assigned treatment with a coin flip and the other half assigned as a control. The half of the scar that was randomly assigned to receive treatment was resurfaced with a fractional 2,940 erbium:YAG laser (MCL31 Dermablate, Asclepion). The parameters used were fluence of 12 J/cm2, 25% cover rate, 1000ms pulse length, and 3 pulses. This covered an area of 13mm x 13mm with each pulse. The approximate depth calculated according to the fluence was 38 micrometers. Only one pass was performed through the center of the wound.

The edges of the wound were then covered in Mastisol (Ferndale Laboratories, Ferndale, MI) and the entire length of the repair was reinforced with Steri-Strips (3M Health Care, St Paul, MN). Finally, a pressure dressing was placed on the site and subjects were instructed to keep the area dry until self-removal in 24 hours while keeping the Steri-Strips in place for 7 days.

Subjects were seen at 7 days following the surgery and then again at 12 weeks postoperatively. A few patients who could not be seen 1 week following surgery were seen at 1 month. High-resolution photographs were taken at each visit with a digital camera (Canon EOS 60D) utilizing a 60-mm lens (Canon EF-S 60mm f/2.8 Macro USM) and compact flash (Integra Mini 300). The wound was evaluated for any sign of dehiscence, infection, hematoma, or other adverse reaction. At the final visit, subjects performed a self-assessment that asked the questions: is there a difference between the two scar halves (yes/no)? If 'yes', which side is better? In addition, patients compared the two halves in regard to erythema, elevation, and similarity to normal skin and asked: is there a difference between the two scar halves (yes/no)? If 'yes', which side is better? A mirror was provided to assist patients with their self-assessment. Patients were offered to have the control side treated with the erbium:YAG laser during this visit as well.

Photographs were evaluated by three blinded dermatologic surgeons. Physicians compared both ends of each scar and rated them as equal or determined that one was better than the other.

RESULTS

Eighteen patients were recruited for the study. Seventeen patients participated in the study and completed the treatment

TABLE 1.

Demographics and Scar Characteristics			
Patient No./ Sex/Age, y	Location	Portion Treated	Scar Length, cm
1/M/79	Left ventral proximal forearm	Lateral	3.2
2/F/41	Left nasal cheek	Inferior	1.5
3/M/33	Left lower back	Inferior-lateral	1.6
4/F/60	Right anterior thigh	Inferior	6.0
5/M/46	Right wrist	Superior	2.2
6/M/60	Left forearm	Lateral	4.1
7/F/39	Left forehead	Lateral	1.5
8/M/62	Anterior scalp	Superior	2.8
9/F/80	Left nasal bridge	Inferior	1.6
10/F/90	Left forearm	Distal	2.0
11/M/59	Right medial supraclavicular	Lateral	5.0
12/M/78	Right lateral cheek	Medial	3.6
13/M/54	Right mid forehead	Lateral	2.9
14/M/63	Left nose	Superior	2.5
15/F/82	Right chest	Medial	2.9
16/M/50	Right axilla	Medial	3.1
17/M/67	Mid forehead	Superior	6.9

FIGURE 1. Patient #11, 3 months after lateral half (left side in image) treated with laser.

FIGURE 2A. Patient #18, 1 month after superior half treated with laser. Patient #18 3 months after superior half treated with laser.

FIGURE 2B. Patient #18, 3 months after superior half treated with laser.

protocol and follow-up (11 males and 6 females). One patient was excluded due to unknown predisposition for keloid formation. The average age was 61.3 years (range, 33–90 years). The average length of repair was 3.1 cm. 8 surgeries were located on the scalp/head and 9 were located on the trunk/extremities. Patient characteristics are reported in Table 1.

There were no incidents of infection, dehiscence, hematoma or necrosis during the study. There were no cases of persistent erythema. The treatments were well tolerated, as the local anesthesia used for the surgery was still in effect, with the only minor side effect after the treatment being erythema which resolved within 2–3 days. 64.7% of the subjects (11 of 17) reported that the treated side was cosmetically superior to the control side. Patients also compared the two sides for elevation, erythema, and similarity to normal skin. 70.6%, 94.1%, and 76.5% of patients believed that the treated side was superior to the control side in regard to elevation, erythema and similarity to normal skin, respectively.

Physician evaluation demonstrated that there was a consensus (2 or more physician agreement) on the treated side being cosmetically superior in 13 out of 17 patients (76.5%). A consensus on both halves being the same was reached on 2 of 17 patients (11.8%). A consensus that the treatment half was worse than the control half was reached on 1 of 17 patients (5.9%).

DISCUSSION

Fractional photothermolysis utilizes the separation of a single laser beam into an array of smaller beams to deliver microscopic treatment zones (MTZs) of thermal injury to the skin. This generates an array of microcolumns of thermal zones that are bordered by normal tissue which permits keratinocyte migration and extrusion of damaged epidermal components to the border of the column of damage. In addition, MTZs selectively damage thermal tissue leading to the formation of new dermal collagen and the repair of tissue defects.[7,8] In this study, we chose to use the higher temperature setting for skin tightening. As previously demonstrated, following laser treatment, several growth factors are released, and cytokines are generated sequentially with varying levels over time; this leads to the coordinated expression of heat shock proteins, matrix metalloproteinases, growth factors, and other mediators that are crucial for early epidermal regrowth and collagen remodeling. Heat shock response, in particular, is responsible for increasing cell proliferation and collagen production speed.[9]

Healing occurs in an orderly pattern. A deviation in this process can result in a scar and can be caused by a variety of factors. Wound healing can be dividing into three main processes: inflammation, proliferation, and remodeling. The inflammatory phase marks the immediate period up to about 96 hours post-incision.[10] During this phase, damaged blood vessels elicit a cellular response, leading to cytokine release, including growth factors such as TGF-β, stress proteins such as heat shock protein (HSP) and endopeptidases such as matrix metalloproteinases (MMP). During the proliferative phase, granulation tissue forms within the wound, and lasts a little over 3 months. Finally, fibroblasts begin to synthesize and deposit collagen, marking the final, remodeling phase.[10,11] Disruptions during this intricate wound healing process may lead to atrophic, hypertrophic, or even keloidal scars. This suggests that any method that assists in the wound healing process may ultimately help create a cosmetically superior, final scar.[12]

Various laser modalities have been studied during the different phases of wound healing with the intention of enhancing the cosmetic appearance of surgical wounds. In a 2014 consensus report, Anderson et al discussed the potential benefits of early intervention with ablative fractional laser resurfacing in helping with wound contracture and healing.[12] In 2018, Karmisholt et al studied the impact of intervention time with non-ablative fractional laser (NAFL) to improve scarring.[13] They demonstrated that treatment applied 1 day before, immediately after or 2 weeks after wounding has the ability to improve the appearance of scars when compared to control scars. Karmisholt et al also studied the utility of 3 NAFL exposures given immediately before surgery, at suture removal and 6 weeks after surgery to correlate with the different phases of wound healing.[14] The split-scar design showed that the treated halves were less erythematous, more pliable and a had a smoother relief when compared to the untreated halves. Using an 810-nm diode-laser system immediately after surgery, Capon et al found that high-dose (80–130 J/cm^2) treated scar halves scored better than low-dose (50–80 J/cm^2) treated scar halves by both surgeons and patients.[15]

This study design was most similar to the study of intraoperative treatment of surgical wound edges with CO2 by Ozog and Moy. Patient self-evaluation in this study demonstrated that 90% of subjects (9 of 10) felt that the treated side was cosmetically superior to the control side, compared to 61.1% of subjects in this study. In addition, physician consensus rating (2 of 3 physician agreement) of scar photographs was 100%, compared to 67% in this study. The difference in results between the two studies can most likely be explained by the decreased efficacy of the erbium:YAG compared to CO2 laser. In studies that directly compared the two laser treatments for facial resurfacing, the CO2 laser was associated with greater efficacy than the erbium:YAG.[16-19] Khatri et al demonstrated that there was no significant difference between subjects who received 5 or more passes of erbium:YAG laser and those who received 2 to 3 passes of CO2 treatment,[16] meaning that more passes of the erbium:YAG over the surgical wound may have had a more significant impact on cosmetic outcome. In addition, the total anatomic depth of tissue necrosis is less with the erbium:YAG laser when compared

to CO2 which in combination with the greater thermal damage achieved with CO2, could explain the inability of intraoperative erbium:YAG to mimic the effects of intraoperative CO2. In addition, with the energy settings used in Ozog and Moy's study, the approximate depth of penetration is 400-450 µm,[17] whereas with the setting we used in this study, the depth of penetration was approximately 38 µm. This suggests that the depth of penetration is the most likely reason for decreased scar prevention with the erbium:YAG laser.

A strength of this study is the randomized, controlled, single-blinded, split-wound study setup with internal controls. Only 7 previous studies have utilized this method when studying the effects of laser initiated in the inflammation phase of wound healing.[3-6, 13-15]

There are several limitations to this study. First, the follow up time of 3 months was relatively short. Wound healing is known to continue up to 6 to 12 months post-surgery and the final outcome of laser treatment might change if reevaluated during this time.[20] In addition, it may have been better for physicians to score the scars with a validated scale when the patients were seen in the clinic rather than photographs of the scars for a more detailed evaluation of aspects of scars such as pliability and thickness. The authors did not believe that a validated scale, such as the Patient Observer Scar Assessment Scale (POSAS), would be of use in this study as the patient would have a hard time delineating items such as pain or itch between the two halves of the scar. Furthermore, the patient was not blinded and therefore the patient-reported outcomes may be biased.

CONCLUSION

Our study demonstrated the clinical efficacy of scar prevention using a fractional erbium:YAG laser immediately after skin suture was performed. A majority of the halves of the scars that received treatment had an improvement in appearance and texture 3 months after surgery. We conclude that this prospective comparative trial demonstrates that early laser treatment performed immediately after surgery can improve the appearance of a surgical scar. An erbium:YAG laser may not be as effective as CO2 laser in reducing scar appearance due to the difference in depth of penetration and thermal damage. Additional studies may be warranted to assess different laser settings with greater depth of penetration to optimize a protocol for scar prevention. This work, along with previous studies of early laser treatment of surgical wounds, could help providers to increase patient satisfaction with scar appearance following a surgical procedure.

DISCLOSURES

The authors have disclosed no relevant conflicts of interest.

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AUTHOR CORRESPONDENCE

Hiren Kolli BS
E-mail:..... kollih@vcu.edu

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Red Deer Umbilical Cord-Derived Stem Cell Conditioned Media Combined With Ablative Resurfacing of the Face

Elika Hoss MD,[a] Ramya Kollipara MD,[b] Marwan Alhaddad MD,[c] Monica Boen MD,[c] Mitchel P. Goldman MD[c]

[a]Department of Dermatology, Mayo Clinic, Scottsdale, AZ

[b]Westlake Dermatology & Cosmetic Surgery, Dallas, TX

[c]Cosmetic Laser Dermatology, A West Dermatology Company, San Diego, CA

ABSTRACT

Background: Laser resurfacing is the gold standard procedure for photodamage, but is not without downtime and risk. Use of periprocedural products containing stem cell conditioned media may improve results and optimize healing.

Study Design: This was a prospective, randomized controlled, double-blind study, evaluating the efficacy and tolerability of red deer umbilical cord-derived stem cell conditioned media (USCCM) cream and serum pre- and post- ablative facial resurfacing.

Methods and Materials: Twenty patients with moderate to severe photodamage were randomized to receive vehicle or USCCM cream and serum pre- and post- ablative resurfacing of the face. Blinded investigators rated healing, tolerability, and efficacy, while subjects rated post-procedure symptoms, tolerability, and satisfaction.

Results: Both the active and vehicle pre-procedure cream were soothing, calming and easy to use by all patients. There was a trend towards decreased facial erythema and crusting in the active versus vehicle group. A greater improvement in wrinkling occurred in the active group. The majority of subjects were very satisfied with the active products. There were no serious adverse events.

Conclusion: Red deer umbilical cord-derived stem cell conditioned media (USCCM) is well tolerated, safe, and efficacious for use pre- and post- facial laser resurfacing.

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INTRODUCTION

Aging is a multifactorial process, leading to changes at every level of the skin. Extrinsic factors such as environmental and ultraviolet (UV) damage lead to accumulation of free radicals, oxidative stress, and DNA damage. Intrinsic factors include reduced cell turnover, as well as loss of collagen, elastin, and hyaluronic acid. In combination, this leads to pigmentation, dull skin tone, textural changes, and fine and deep skin rhytides.[1-3] Laser resurfacing remains the gold standard to improve signs of photodamage and aging, but despite advances in technology, the procedure is often carries a long healing time, patient discomfort, and post-procedure erythema.[4-5]

A novel rejuvenation and healing system (Calecim® Multi Action Cream and Professional serum, Cell Research Corporation, Singapore) utilizes red deer umbilical cord lining mesenchymal stem cell conditioned media (USCCM) to optimize healing post procedure. This patented protein mix contains growth factors, cytokines, amino acids, peptides, and extracellular matrix proteins, to aid in wound and tissue healing processes, as well as improve fine lines, elasticity, pigmentation, and erythema.[6-7]

In this prospective, randomized, controlled, double-blind clinical trial, the authors analyze the efficacy and tolerability of USCCM cream and serum compared to vehicle pre- and post-ablative resurfacing of the face.

MATERIALS AND METHODS

The study was approved by a centralized Institutional Review Board and conducted in accordance with Good Clinical Practices conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

Participants

Twenty healthy subjects, aged 36–70, with skin type I to IV, with moderate to severe photodamage, graded as Class II–III and Score 4–9 on the Fitzpatrick-Goldman Classification of Wrinkling and Degree of Elastosis Scale (Table 1) were eligible for enrollment. Subjects were excluded if they were pregnant or breastfeeding; had systemic steroid use, dermabrasion, deep chemical peel, non-ablative laser, ablative laser, microfocused ultrasound, light or radiofrequency treatment to the face within 6 months; had microdermabrasion or light to medium chemical

TABLE 1.

Fitzpatrick-Goldman Classification of Wrinkling and Degree of Elastosis Scale			
Class	**Wrinkling**	**Score**	**Degree of Elastosis**
I	Fine wrinkles	1-3	Mild (fine textural changes with subtly accentuated skin lines)
II	Fine to moderate-depth wrinkles, moderate number of lines	4-6	Moderate (distinct popular elastosis [individual papules with yellow translucency under direct lighting] and dyschromia)
III	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	7-9	Severe (multipapular and confluent elastosis [thickened yellow and pallid] approaching or consistent with cutis rhomboidalis)

peel within 30 days; had received any topical product containing tretinoins or derivatives, alpha-hydroxy acids, salicylic acid, and vitamins C or E (includes derivatives thereof) on the face within 14 days or at any time during the trial; had recently excessive exposure to sunlight or artificial UV light, or expectations of tanning during the time of the study, or used self-tanner within 7 days; had used a systemic retinoid within the past 1 year; history of keloidal scarring; allergy to product ingredients, benzocaine, lidocaine, tetracaine, PABA (para-amino benzoic acid), or other local anesthetics of the amide or ester family sedation medication; active bacterial or viral infection in the treatment area; or history of skin condition/disease that might interfere with the diagnosis or evaluation of study parameters.

Intervention

All subjects received ablative carbon dioxide (CO_2) resurfacing use a 10,600nm Ultrapulse Encore laser using the ActiveFx mode (Lumenis Inc., Santa Clara, CA), consisting of one pass over the face, and two passes in the perioral and periorbital area (Energy: 100mJ; Power: 60 watts; Density: 5). Prior to the laser procedure, mild sedation with 1–2 mg lorazepam was achieved at the discretion of the physician. Anesthesia included topical 23% lidocaine / 7% tetracaine ointment, facial nerve blocks using 1% lidocaine with epinephrine 1:100,000, and infiltration fluid using a dilute lidocaine mixture of 3cc of 1% lidocaine with epinephrine 1:100,000 and 7cc of 0.9% sodium chloride. Prophylactic antimicrobials included minocycline 100mg twice daily and valacyclovir 500mg twice daily for 10 days starting the evening prior to the procedure.

Subjects were randomized to two groups, the control group (n=5) and the USCCM group (n=15). In the control group, pre-procedure cream (vehicle), and post-procedure cream and serum (vehicle) were used, while in the USCCM group pre-procedure cream (Calecim® Multi-Action Cream), and post-procedure cream and serum (Calecim® Multi-Action Cream and Calecim® professional serum) were used. The only difference between the vehicle products and active products was the addition of red deer umbilical cord protein cytokines and growth factors as the active ingredient. Both the subjects and evaluating investigator were blinded to the treatment halves. Pre and post-procedure regimen is summarized in table 2.

Assessment

Subjects were evaluated in the office on post-procedure days 1, 5, 7, 14, 21, and 30 ± 3 days. The Canfield VISIA photography system was utilized at all visits from baseline to end of study.

At each post-procedure visit, a blinded investigator graded the percent of surface area healed along with grading of erythema, edema, exudation, and crusting on a 5-point scale (none (0) to severe (4)). An overall healing grading (poor (0) to excellent (4)) was given, along with a comparative score based on the investigators past experiences with post-resurfacing healing. Additionally, investigator assessment of tolerability was rated on a 10-point scale (0=none to severe (9)) for erythema, edema, and dryness. At the end of study, an overall photodamage/wrinkle score was given based on the Fitzpatrick-Goldman wrinkle scale, in addition to a global improvement assessment score (0 = Worse, 1 = No improvement, 2 = Mild improvement (less than 25%), 3 = Moderate improvement (between 25%–50%), 4 = Marked improvement (more than 50%).

Subjects rated symptoms of pain, itching, tightness, oozing, crusting, healing, and tolerability at each post-procedure visit. Satisfaction survey on pre-procedure cream, and post-procedure cream and serum was completed at the end of use. Patient self-assessment questionnaire was completed on day 30.

TABLE 2.

Pre- and Post- Ablative Resurfacing Regimen	
Pre-procedure (4 weeks)	1. Cetaphil cleanser twice daily 2. Application of pre-procedure cream twice daily 3. EltaMD UV Daily Broad-Spectrum SPF40 in the morning, with re-application throughout the day
Post-procedure	1. 20 minute vinegar soaks every 2 hours while awake* 2. Application of post-procedure serum after each soak 3. Application of Vaniply ointment for dryness as needed
Post-healing (initiated once skin fully healed)	1. Cetaphil cleanser twice daily 2. Application of post-procedure serum twice daily 3. Application of post-procedure cream twice daily 4. EltaMD UV Daily Broad-Spectrum SPF40 in the morning, with re-application throughout the day

*Vinegar soaks: 2 teaspoons white vinegar in 16 ounces distilled water

Statistical evaluation was performed with Microsoft excel 2013. The two-tailed student's t-test was utilized to determine the difference in means between groups.

RESULTS

A total of 20 subjects, 19 female, 1 male, aged 67.0 ± 7.2, and range 50.9–68.9 years completed the study (Table 2). Prior to the ablative fractional CO2 treatment, all patients were pre-treated with active and vehicle cream twice daily for 30 days and in both groups 100% noted that the creams felt comforting on the skin, felt soothing and calming, easy to use with sunscreen, and easy to use with makeup. A majority of patients (90%) noted that the active and vehicle creams left the skin feeling hydrated. There was no statistically significant difference in the active and vehicle cream in the subject pre-procedure cream questionnaire.

Per investigator evaluation there was a trend to improved erythema and crusting in the active cream and serum group, but this was not statically significant (Figure 1 and 2). On post-procedural day 1, the active group had a lower score on the five point investigator tolerability score in perioral erythema (1.67 active vs 1.8 placebo), periorbital erythema (1.6 vs 1.8), overall facial erythema (1.2 vs 1.6), and facial crusting (2.13 vs 2.4), but these were not statistically significant (Figure 1–3). Similarly, on post-procedure day 5, the active group had a lower score on the five point investigator tolerability score in overall facial erythema (1.53 vs 2), and facial crusting (2 vs 2.5), but these were not statistically significant. On post-procedure day 7, the active group had a lower score in perioral erythema (2.2 vs 2.4) and periorbital erythema (1.8 vs 1.6), though, these did not reach statistical significance. There was no difference in the healing times between the active and vehicle creams. Active and vehicle products were similarly tolerable by investigator evaluation of erythema, edema, and dryness.

TABLE 3.

Patient Characteristics		
	Control	Active
Subjects	5 (female)	15 (14 female, 1 male)
Age (average)	60.6 years (50–68)	57.1 years (50–65)
Fitzpatrick Skin Type	Type I: 1 Type II: 4	Type I: 4 Type II: 9 Type III: 2
Fitzpatrick-Goldman Photodamage Score	Wrinkling 2, Elastosis 6: 0 Wrinkling 3, Elastosis 7: 4 Wrinkling 3, Elastosis 8: 1	Wrinkling 2, Elastosis 6: 3 Wrinkling 3, Elastosis 7: 5 Wrinkling 3, Elastosis 8:

Number of patients with skin type or photodamage score listed after category.

Both the active and placebo group had a decrease in the Fitzpatrick-Goldman Wrinkling and Elastosis score, with an average improvement of 44% in elastosis, with an average score of 7.2 out of 9 that decreased to an average of 4 at day 30 (Figure 3). The active cream and serum group showed a greater decrease in wrinkling score than placebo with a decrease of 42% from baseline in the active cream and serum group (2.87 baseline to 1.67 at day 30) versus a 33% decrease in wrinkling in the vehicle group (7.27 baseline to 4.07 at day 30). This difference was not statistically significant.

Subjects found the active products to be more tolerable on the treatment day than the vehicle alone, with less burning (P=0.04), stinging (P=0.04), dryness (P=0.54), and itching (P=0.3). Pain, tightness, oozing, and crusting were similar between groups during the remainder of the healing phase. Subject satisfaction

FIGURE 1. Subject who received vehicle products at baseline, post-procedure day 1, day 5, day 7, and day 14.

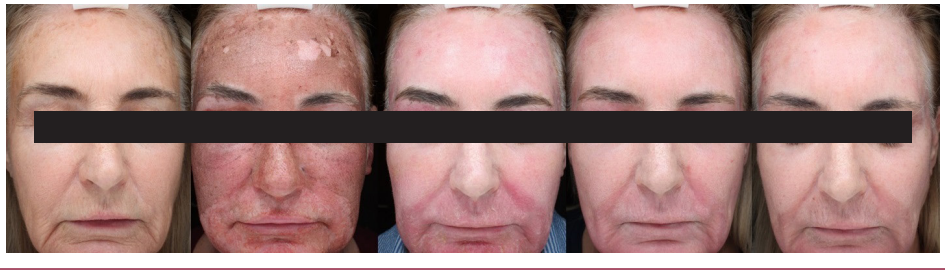


FIGURE 2. Subject who received active products at baseline, post-procedure day 1, day 5, day 7, and day 14.

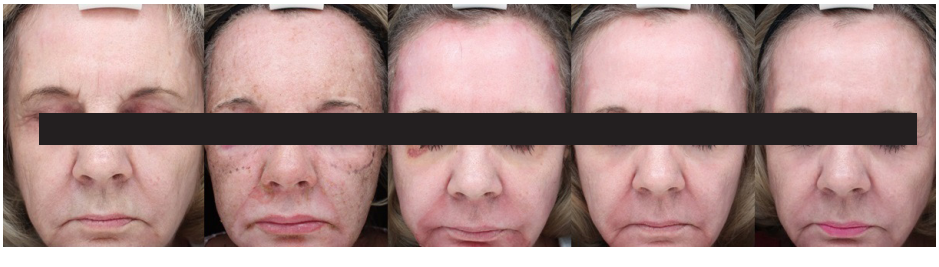
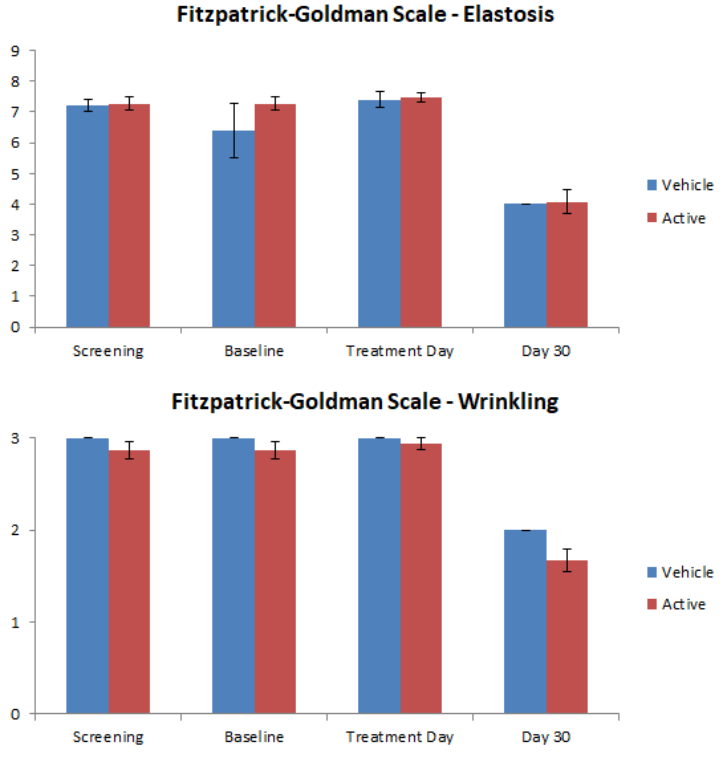


FIGURE 3. Blinded investigator scoring of the Fitzpatrick-Goldman Wrinkling and Elastosis Scale at screening, baseline, treatment day, and day 30.



with healing and skin quality also trended towards higher scores for the active products versus vehicle products at all time points, although this was not statistically significant. The active and vehicle post-procedure serum and cream were both tolerated, with a trend towards favorability of the active serum and cream in regards to post-procedure skin dryness, tightness, and sensitivity. 93.3% and 100% of patients graded their overall experience with the active post procedure serum and cream as somewhat satisfied to very satisfied, respectively.

Assessment of post-treatment adverse events consisted of one patient in the vehicle group with prolonged erythema which resolved after treatment with a 595 nm pulsed-dye laser and one patient in the active group with post-inflammatory hyperpigmentation on post-procedure day 30, after spending over four hours in the sun after the skin had healed. This resolved with use of hydroquinone 6% pads, increase in sunscreen use, and sun avoidance. There were no cases of scarring or infection.

DISCUSSION

While ablative CO2 resurfacing is well recognized as the gold standard treatment for photodamage and rejuvenation, peri-procedural care varies widely amongst laser physicians. Use of petrolatum or dimethicone-based ointments are often utilized post-procedure due to lack of irritants, chemicals, fragrances, and allergens, but these do not have any added benefit in improving healing or enhancing post-procedure outcomes.

Normal wound healing after ablative CO2 resurfacing involves a complex cascade of hemostasis, inflammation, collagen breakdown, and neocollagenesis. Re-epithelialization relies on interfollicular stem cells between hair follicles, as well as stem cells recruited from deeper structures such as hair follicles and sebaceous glands.[8] More recently, use of stem cell technology has been studied in the treatment of chronic wounds and post laser resurfacing procedures, given their ability to secrete protein growth factors and cytokines which expedite and improve the healing process.[9] In a randomized, split face study of 22 patients, adipose-derived stem cell conditioned media was shown to decrease transepidermal water loss, and melanin index compared to control after application for one hour after fractional ablative CO2 resurfacing. Biopsy in one patient also showed increased dermal collagen and elastin on the treatment side.[14] Higher concentrations of stem cell media have also been associated with faster reepithelialization and less inflammation after resurfacing.[16]

This double-blind, randomized controlled study evaluated the efficacy and tolerability of USCCM pre- and post- laser resurfacing of the face, and the findings indicate that it is a favorable option for post resurfacing care. The blinded investigator healing scores indicate that USCCM may decrease post procedure erythema and crusting. Additionally, subjects found the active product to be more tolerable with a trend towards less burning, stinging, dryness, and itching, and overall

healing. Both groups tolerated the products well. Pre-procedure active and vehicle cream were similarly comforting, soothing, hydrating and easy to use on normal skin. Post-procedure, the active serum and cream were found to be favorable in regards to dryness, tightness, and sensitivity in comparison to the vehicle.

Additionally, USCCM may also enhance the results of ablative CO2 resurfacing. At day 30 a greater decrease in wrinkling was seen in the active group than the vehicle group and similar improvement was seen in elastosis. Subjects also reported a greater improvement in skin quality at all time points with use of the active products. While these changes were not statistically significant, the follow up period was short, as this was primary a wound-healing study. It is well-known that continued changes such as thickening of epidermis, increase in collagen, and decrease in solar elastosis is seen up to 24 months after ablative CO2 resurfacing, and how this may be enhanced with continued protein cytokine and growth factor use is intriguing.[10-12]

No cases of post-procedure erythema were seen in the active group, while one was seen in the vehicle group, suggesting that use of USCCM may be effective at decreasing erythema, as reported with use of human cell-conditioned media in previous studies.[13] One case of post-inflammatory hyperpigmentation was identified in the active group and thought to be secondary to excessive post-procedure sun-exposure and unrelated to treatment use. This resolved with standard treatment measures.

Limitations of this study include the small sample size and short term follow-up. While the active products trended towards improved healing, efficacy and satisfaction, statistical significance was not demonstrated between the active and vehicle groups. One possibility is that the stabilized, lipovesicular technology in the proprietary vehicle cream may have some healing potential.[7] Additionally, since long term changes occur for up to 2 years post resurfacing, continued use of USCCM may further enhance these results. The beneficial effects of stem cell proteins post resurfacing have been demonstrated by several clinical studies.[14-18] Further studies in this arena are needed to optimize post-procedure care and enhancement of long-term outcomes.

CONCLUSION

This study found the application of pre- and post- procedure USCCM to be well tolerated, safe and efficacious after ablative CO2 resurfacing. Use of the active products trended towards improved skin quality, healing, and increased patient satisfaction. Further large scale studies with longer follow-up periods are needed to better understand the role of USCCM in peri-procedural outcomes.

DISCLOSURE

Mitchel P. Goldman MD is a consultant for CellResearch Corporation. None of the other authors have relevant conflicts to declare.

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AUTHOR CORRESPONDENCE

Elika Hoss MD
E-mail:..... elikahoss@gmail.com

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ORIGINAL ARTICLE

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Wound Healing Treatments After Ablative Laser Skin Resurfacing: A Review

Hayley Leight-Dunn MD,[a] Margot Chima MD,[a] Elika Hoss MD[b]

[a]Icahn School of Medicine at Mount Sinai, Department of Dermatology, New York, NY

[b]Mayo Clinic, Department of Dermatology, Phoenix, AZ

ABSTRACT

Laser resurfacing has progressed since the 1980s to treat a variety of medical and aesthetic indications with ever-evolving safety parameters. While laser technology has evolved to provide a more favorable safety profile and decrease wound healing time, advances in post-procedure healing agents have also helped to mitigate adverse effects, such as persistent erythema, dyspigmentation, acneiform eruptions, dermatitis, infections, and scarring. We reviewed the evidence of growth factors, stem cells, silicone and silicone polymers, botanical based treatments, fatty acids, probiotics, and closed dressings on post-ablative laser skin resurfacing. All reviewed agents demonstrated some evidence in improving post-procedure outcomes, albeit mixed in many cases. Additionally, these studies contain small numbers of participants, vary in type, strength, and clinical indication for which the resurfacing laser was used, and have differing postprocedural evaluation protocols and assessments. This highlights a need for standardization of clinical studies and the importance of choosing an optimal postprocedural skincare plan depending on every unique clinical scenario.

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INTRODUCTION

Laser resurfacing has progressed since the 1980s to treat a variety of medical and aesthetic indications with ever-evolving safety parameters. While laser technology has evolved to provide a more favorable safety profile and decrease wound healing time, advances in post-procedure healing agents have also helped to mitigate adverse effects, such as persistent erythema, dyspigmentation, acneiform eruptions, dermatitis, infections, and scarring. We reviewed the evidence of growth factors, stem cells, silicone and silicone polymers, botanical based treatments, fatty acids, probiotics, and closed dressings on post-ablative laser skin resurfacing. All reviewed agents demonstrated some evidence in improving post-procedure outcomes, albeit mixed in many cases. Additionally, these studies contain small numbers of participants, vary in type, strength, and clinical indication for which the resurfacing laser was used, and have differing postprocedural evaluation protocols and assessments. This highlights a need for standardization of clinical studies and the importance of choosing an optimal postprocedural skincare plan depending on every unique clinical scenario.

First introduced in the 1980s, laser resurfacing has progressed throughout the years to treat a variety of medical and aesthetic indications with ever-evolving safety parameters. The original continuous wave carbon dioxide (CO2) laser (10,600 nm) vaporized epidermal tissue, but had erratic depths of ablation and caused significant thermal damage to adjacent normal skin leading to high rates of post-procedure scarring and pigmentary changes.[1,2] Further advances in technology and safety led to discontinuous ablative lasers, with high energy and short duration laser pulses, that would rapidly ablate tissue while limiting the surrounding thermal damage.[1] While these lasers had superior clinical results and a more favorable safety profile, significant down time and persistent pigmentary changes still limited the mass use of these lasers.[1] Developed in the early 2000s, fractionated ablative laser technology admixed focused laser beamlets with intervening areas of normal, untouched epidermis, improving laser safety, and decreasing wound healing time.[1]

The clinical efficacy of ablative laser technology lies in the vaporization of normal tissue structures, triggering a wound healing response in the body with neocollagenesis. Normal healing proceeds through a complex cascade of hemostasis, inflammation, proliferation, and remodeling, driven largely by the local cytokine milieu. After the acute inflammatory phase, recruited fibroblasts synthesize new collagen while the keratinocytes must migrate from wound edges or proliferate from stem cell reserves to epithelize and recreate the epidermal barrier.[3] Full laser ablation destroys epidermal stem cell populations, thus stem cells must be recruited from deeper structures like hair follicles and sebaceous glands. In fractionated ablative technology, the intervening areas of normal epidermis can contribute to the stem cell reserve synergistically with the deeper skin structures and significantly decrease overall healing time.[1]

Despite the advances in technology, laser ablation creates large injuries to the skin and is not without complications. Adverse effects seen include persistent erythema, dyspigmentation, acneiform eruptions, dermatitis, infections, and scarring.[2] While operator skill level, appropriate patient selection, and correct laser settings for desired outcomes are all important, meticulous postoperative care cannot be undervalued. Historically, uses of petrolatum or dimethicone-based ointments have been utilized during healing due to lack of fragrances, chemicals, irritants or allergens. More recently, numerous healing agents have become commercially available, such as growth factors, stem cell, peptide and silicone-based topicals for ablative laser post-procedure healing, with the intent to improve healing and/or enhance post-procedure outcomes. This review will describe and compare many of the available healing agents in the recent literature.

Growth Factors

Growth factors are the major mediators of the wound healing process. Through various connections with peptide receptors, they can stimulate and synchronize wound inflammation, angiogenesis, and the production of new epidermal and dermal tissue for wound reepithelization. [4,5]

Epidermal growth factor (EGF), in particular, is a well-known mitogenic cytokine released from platelets and keratinocytes.[4,5] EGF induction of keratinocyte migration and proliferation has shown promise in the healing of chronic ulcerative wounds.[6,7]

The efficacy of EGF based topical treatment after aesthetic procedures has been limited. A randomized split face study with 19 healthy patients subjected to fractional carbon dioxide laser resurfacing (FxCR) found no significant differences in erythema, duration of scab shedding, or post inflammatory hyperpigmentation between the EGF ointment-treated side versus the petrolatum control.[5]

A newer agent in the treatment armamentarium, platelet rich plasma (PRP), obtained from a centrifuged preparation of autologous blood, contains a dense medium of multiple concentrated growth factors that has been shown to improve wound healing outcomes, increase cellular recruitment of dermal stem cells, and aid in tissue regeneration.[8-10]

A recent split-face randomized clinical trial with twenty-five patients compared outcomes after FxCR for acne scarring with and without postoperative adjuvant intradermal PRP injections versus intradermal saline injections. Skin biopsy immunohistochemistry showed increased transforming growth factor beta 1 and 3 (TGF-β1 and TGF-β3), c-myc, tissue inhibitors of metalloproteinases (TIMP), and collagen 1 and 3 expression in the PRP treated side when compared with the control side. Clinically, patients had statistically significant improved efficacy and early skin recovery rates with milder adverse effects with the laser/PRP combination. Additional endpoints evaluated fibroblast and keratinocyte tissue culture exposed to laser irradiation and subsequent PRP. Increased expression of collagen, TGF-β, and EGF expression in the tissue culture suggest that PRP may accelerate the skin repair process.[9]

Synergistic healing results with FxCR and PRP were also shown in a split-arm study of 26 patients in 2011 by Jung-Im et al. Patients underwent ablative resurfacing to each inner arm followed by randomly assigned application of either PRP or normal saline to the wound site. The PRP-treated arm had a reduction in overall transepidermal water loss (TEWL) and a decreased erythema index (EI) and melanin index (MI) indicating decreased post-procedure erythema and less potential post-inflammatory pigmentation. Biopsy specimens demonstrated increased collagen bundles from the PRP-treated side, hypothesized to be from PRP induced stimulation of stem cells and extracellular matrix component synthesis.[11]

Stem Cells

Stem cells provide a unique and innovative therapeutic potential to accelerate wound healing. Known for the ability to self-renew and differentiate into multiple cell lineages as well as provide a lush source of regenerative cytokines and growth factors, stem cells are currently being studied to aid in wound and tissue healing processes. While there remain many obstacles to mainstream clinical use, current research in dermatology and other fields are attempting to identify the best stem cell populations for clinical therapeutics and the optimal vehicle delivery systems to aid in tissue regeneration.[12] Both adipose-derived stem cells (ADSCs) and human cell-conditioned media with neonatal cells have shown promise in ablative laser posttreatment wound repair.[13-16]

ADSCs are mesenchymal pluripotent cells that have a multifaceted ability to promote wound healing. In vitro studies by Kim et al showed ADSCs have the ability to stimulate the migration of human dermal fibroblasts and influence dermal fibroblasts and keratinocytes with paracrine growth factor signaling.[17] Animal studies with topical conditioned media of ADSCs demonstrated decreased wound size and a more rapid reepithelization of the wound bed, indicating promise of ADSCs in skin regeneration.[17,18] Clinically, allograft adipose-derived stem cell conditioned media (ADSC-CM), which is devoid of cells, is advantageous for wound healing. This minimizes immunogenicity and negating the need for surgical procedures to harvest stem cell populations, while still providing the wound healing properties inherent to mesenchymal stem cells.[14,15]

In vivo research by Bing-Rong et al demonstrated wound healing properties of ADSC-CM on 19 human subjects. FxCR was performed on each patient's bilateral inner arms with the

application of allograft ADSC-CM to one randomly selected arm for one hour. The control arm had fetal bovine serum-free Dulbecco's modified Eagle's media (FBS-free DMEM) applied for one hour. The treatment arm had significantly decreased TEWL, EI, and MI at multiple follow-up endpoints, as well as biopsy-proved increased messenger RNA (mRNA) expression of type III procollagen at the 3-week post-treatment time. There was no significant difference in the control or treatment group gross elasticity of the skin.[14]

Bing-Rong et al also used the same ADSC-CM to treat facial atrophic acne scars and skin rejuvenation subjects. Twenty-two subjects of both sexes were treated with FxCR to facial skin, one pass for the skin rejuvenation group and two passes for the acne scarring group for a total of 3 treatment sessions. After each treatment, each subject had one side of the face randomly selected to receive ADSC-CM topically applied for one hour. The control side of the face received FBS-free DMEM for one hour. Results showed statistically significant improvement in subject satisfaction, and skin elasticity and hydration. Significant decreases in TEWL and MI were seen in the ADSC-CM combined with FxCR treatment side. Skin biopsy from one patient showed ADSC-CM side had increased dermal collagen and elastin density than the DMEM treated side. There were no significant differences in adverse events between the groups.[15]

Human cell-conditioned media (hCCM) has also been used as a wound healing agent after FxCR. By growing human neonatal fibroblast cells under embryonic-like environmental conditions, the cells have been stimulated to produce cytokines, growth factors, and extracellular matrix material such as vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and interleukin-8 (IL-8) in types and amounts similar to that of native fetal cells, showing promise in post-ablative wound healing.[13,16]

In a pilot clinical randomized, double-blind, placebo-controlled study, forty-nine participants received either a hCCM-containing gel (ReGenica Facial Rejuvenation Complex, Histogen Aesthetics, San Diego, CA) or a placebo gel formulation without the active HCCM ingredient after undergoing ablative fractional erbium laser to the peri-oral and peri-ocular regions. The remainder of the face was treated with nonablative fractional erbium laser. While not statistically significant, the treatment group with the hCCM-containing gel had greater improvement in erythema and re-epithelization in the peri-oral and peri-ocular treated areas by day 7 when assessed by blinded clinical evaluation and mexameter data. Additionally, the treatment group had less use of rescue petrolatum ointment than the control subjects and no significant differences in adverse events.[13]

Subsequently, Zimber et al performed a split-face trial with 42 subjects who underwent ablative fractional erbium laser in the peri-oral and peri-ocular regions and nonablative fractional erbium laser on the remainder of the face. The subjects were randomly assigned to receive either differing concentrations of hCCM-containing gel (× 0.1, × 1.0, × 10.0) on one side of the face and a control gel treatment devoid of soluble hCCM to the other half of the face. Blinded dermatologist evaluation of crusting on posttreatment day 7 showed a dose-response trend with the higher concentrations of gel having a greater impact on subject healing. Measurements of TEWL with a Vapometer unit revealed a statistically significant difference between the control and active gels on days 3 and 7, indicating more rapid reepithelization and return to normal skin functioning. Biopsy specimens taken 14 days post procedure showed a more normal appearing epidermal structure and less inflammation in the treatment arm.[16]

Silicone and Silicone Polymers

Silicone based topical treatments have also garnered some interest in postprocedure wound care. Over 20 years ago, Suarez and Fulton demonstrated rapid healing of facial skin after CO2 laser resurfacing when using an occlusive silicone face sheet for 5 days postprocedure. The occlusive mask led to rapid wound reepithelization both clinically and histologically within 1 week as well as an improved patient experience with decreased pain and swelling. While the facial mask had technical difficulties, such as retraction of the dressing, it was very well tolerated by subjects.[19]

Silicone based polymers have also been used in other non-occlusive topical treatments for wound healing. A novel procedure kit containing multiple skin care products by Alastin, utilizes TriHex Technology™, which contains a tripeptide and hexapeptide formulation within a dimethicone cross-polymer base that can remodel the extracellular matrix (ECM) to promote neocollagenesis and neoelastogenesis, regulate collagen fibrillogenesis and provide antioxidant protection to the skin.[20,21] The healing system can work synergistically with laser resurfacing to stimulate production of the ECM components while also accelerating the skin repair process. In a small clinical study, 15 subjects underwent intense pulsed light (IPL) and/or pulsed dye laser (PDL) with q-switched alexandrite laser, followed by FxCR to the full face. From 3 weeks preprocedure until 12 weeks postprocedure, the treatment group washed their face with a gentle cleanser twice daily and then applied the tripeptide/hexapeptide gel, tripeptide/hexapeptide moisturizer, and sunscreen. The control group used similar facial cleansing guidelines but applied a petrolatum-based moisturizer and sunscreen. Blinded investigator evaluation showed the TriHex Technology™ formulation had superior wound healing rates, demonstrating statistical significance by day 7. Additionally, subjects in the treatment group had less erythema and exudate in the first postprocedure week and improved patient symptomatology. The skin care products were highly rated by subjects on postprocedure questionnaires.[21]

Botanical-Based Treatments

Botanical-based skin care products are popular in society and have shown promise in FxCR postprocedure wound healing. In a comparative double blinded, split-face study by Chapas et al, a novel plant-based hypoallergenic ointment (Doctor Rogers RESTORE® Healing Balm) was compared to a lanolin containing petroleum-based ointment (Aquaphor® Healing Ointment) in facial FxCR postprocedure wound care. Doctor Rogers RESTORE® Healing Balm contains glycerin, a potent bactericidal humectant, and castor seed oil, which renders anti-inflammatory and wound healing properties to the product.[22] Ten male and female participants were instructed to apply the randomized blinded products, to respective halves of their face every 4 hours from days 0–7 with the option of continuing application from days 8–14. Blinded investigator ratings of erythema, edema, crusting, exudate, and overall percentage healing showed a greater overall healing trend toward the plant-based ointment, albeit not statistically significant. Notably, 90% of patients preferred and were more likely to recommend the plant-based ointment over the petroleum-based ointment.[22]

In a split-face, triple-blinded clinical study by Tempark and Lueangarun,[23] a non-steroidal anti-inflammatory agent MAS063DP(Atopiclair® lotion, Sinclair Pharma Srl, Milano, Italy) was compared to 0.02% triamcinolone acetonide (TA) milk lotion following a single pass of FxCR to 16 subjects with bilateral facial atrophic acne scarring. Participants were all skin phototypes III and IV and applied the blinded topical treatment to the assigned facial half twice a day for one-week post procedure. Objective biometric measurements of hemoglobin index, MI, and textural improvement showed no significant difference between sides at any follow up visit. Expert panel photographic assessment did not reveal any difference between sides with respect to erythema, edema, crusting and dryness, albeit both groups had significant improvement with these criteria from day 3 to day 30 postprocedure. Patient subjective assessment did not show differences between groups.[23]

MAS063DP has multiple botanical active ingredients including vitis vinifera (grapevine) extract, telmestine, and 2% glycyrrhetinic acid (GrA) to promote wound reepithelization and minimize inflammation and pigmentation. Vitis vinifera has antioxidant and antiprotease activity, while telmestine can prevent epidermal barrier breakdown through the inhibition of metalloproteinases. GrA can stimulate cutaneous hydrocortisone activity and is a known potent tyrosinase inhibitor, which may help to prevent post inflammatory hyperpigmentation after FxCR.[23] While the clinical and biometric results in the study were equivocal, MAS063DP provides a viable alternative to topical steroids with similar healing outcomes and patient satisfaction.

Not all botanical based treatments have shown promise in fractional resurfacing wound care. Arnebia euchroma, an Iranian traditional medication used in burn wounds, contains shikonin and alkannin rendering anti-inflammatory, anti-microbial, and pain-relieving properties to the compound.[24] In a split-face, single center study of 26 patients with facial atrophic acne scarring undergoing FxCR, wound care with petrolatum alone demonstrated statically improved wound appearance scores and less erythema and crusting as compared to the Arnebia euchroma ointment (AEO). AEO was also associated with an increased sensation of dryness by participants and was less favored by the subjects.[24]

Fatty Acids

Omega-5-fatty acids, including class member, conjugated linolenic acid (CLA), are known to have potent antioxidant and anti-inflammatory properties.[25-27] While CLA has already shown promise in other inflammatory conditions, Goldman and Wu first demonstrated the ability of a novel topical compound with a stable CLA formulation that is safe and effective for epidermal regeneration.[26-28]

In this clinical study, 34 subjects underwent FxCR; laser settings were decided for each patient based on pre-existing wrinkling and elastosis. After the procedure, the test group applied a two-phase system (occlusive ointment for 2 weeks, followed by repair serum and healing cream for 2 weeks) of CLA based products derived from pomegranate oil extract (Pomega MD™, Pomega Inc., San Anselmo, CA). The control group used 1% dimethicone ointment (Vaniply, Pharmaceutical Specialties Inc., Rochester, MN) for the same duration. Evaluations included a blinded evaluator assessment of wrinkling and elastosis, patient graded symptomatology, and blinded evaluation of erythema, edema, crusting, and exudate. The CLA regimen showed significantly reduced edema on day 3 and patient reported itch on days 1 and 3. Both treatments resulted in improved wrinkling and elastosis postprocedure, albeit no significant difference existed between groups.[27] Based on the results of this study, CLA is a safe and alternative healing agent for laser treated skin.

Probiotics

Skin microflora play a triggering role in certain dermatologic conditions such as atopic dermatitis and acne vulgaris.[29] In light of this knowledge, recent research has evaluated the role of probiotics on skin health and their ability to reduce skin inflammation. In a novel study out of Italy by Giuliani et al, a topical preparation probiotic cream was evaluated for healing properties after ablative resurfacing. Sixty-two patients underwent FxCR on the face and hands for conditions ranging from keratosis, rhytids, shallowness, and skin texture irregularities. Subjects laser protocols and treatment areas differed among participants. Each person underwent 1–4 laser sessions at 2–3-month intervals apart. The treatment group applied a cream with probiotic active principles (Derma ACB) mixed in a base cream (CERABEST™) 2 times per day for 2 weeks after each procedure. Control subjects applied a

topical antibiotic cream for 3 days and a HA based cream twice a day for 15 days post procedure. At follow up appointments 1, 2, and 4 weeks postprocedure, 3 external researchers evaluated the clinical response and assessed the treatment cream effect on swelling and erythema. Clinical evaluation of results and skin texture as well as patient subjective assessment failed to show any difference between treatment and control groups.[29] However, the treatment cream showed a statistically significant reduction in erythema resolution and swelling resorption compared to the control subjects,[29] indicating this probiotic cream may potentiate wound healing.

Oil in Water Emulsions

Trolamine/sodium alginate topical emulsion, Biafine Topical Emulsion (BTE) (OrthoNeutrogena, Los Angeles, CA), has shown promise as a wound healing agent after Mohs micrographic surgery and cryosurgery.[30,31] The formula provides an occlusive and moist environment ideal for superficial wounds, ulcerations, first-degree and second-degree burns, graft site management, and radiation dermatitis, among other indications.[31,32] Clinical research has shown that BTE has the ability to stimulate macrophage recruitment, decrease dermal edema and increase epithelial cell proliferation, making it appear to be an ideal candidate for postlaser resurfacing.[32] However, the emulsion has shown less than straightforward results in clinical practice.

In a small, blinded split-face study of 30 patients with erbium resurfacing, BTE topical application outperformed white petroleum in physician assessment of erythema and edema on day 2 and also in physician global reepithelization assessment on days 2, 4, and 6. There was no significant difference in adverse effects.[32]

In contrast, the results of a more recent head-to-head clinical trial of BTE versus Aquaphor Healing Ointment (AHO) paled in comparison. Twenty subjects with perioral rhytids received FxCR followed by the application of either product 4 times daily in a split-face fashion. AHO had superior results in many measured parameters including improved epithelial confluence, reduced crusting and scabbing of the wound bed and notably, superior subject symptomatology scores and product preference.[31] General wound appearance was also significantly improved with AHO on days 2 and 7.[31] While BTE has shown improvement in other dermatologic procedural outcomes, further research is needed to justify using this agent over the current postlaser standards of care.

Closed Dressings

Open dressings are traditionally used in post ablative laser procedures. They often consist of distilled water or acetic acid soaks followed by application of petroleum-based ointments or creams.[33] They are relatively inexpensive, but are time consuming for the patients. Additionally, open dressings are prone to crusting, increased susceptibility for infection, and can lead to the development of contact allergies.[22,33]

Closed dressings are occlusive to the wounded skin and help to facilitate rapid wound healing, while decreasing eschar and crust formation on the wound.[33] Hydrogels have shown promise in postprocedure wound care. Dermaphase® hydrogel dressing mask (Dermalabs Inc., Miami Beach, FL) contains high levels of glycerin and polyacrylamide, allowing the dressing to absorb excess wound fluid, and provide immunomodulating and anti-microbial properties.[22,33] Rendon and Okan compared the clinical outcomes in a split-face study after full-face Er:YAG laser resurfacing when applying the hydrogel mask compared to a placebo Vaseline® cream (VC) in 15 female patients.[33] The hydrogel dressing (HD) was applied postprocedure and changed on days 3 and 4. The patients were instructed to cleanse the other half of the face with a vinegar and water solution and apply VC multiple times per day. At multiple follow-up visits, the HD significantly shortened time to reepithelization and decreased subjective pain and itch scores among participants. Additionally, the formation of crusting was significantly lower on the HD treated facial half. Early scores for erythema and edema were less for the VC side, but no significant differences were noted at the 1-month follow-up results. There was also no significant differences in pigmentation score and no infections noted in either group.[33] In this trial, the occlusive dressing expedited wound healing and improved patient symptomatology greater than the traditional open dressing technique.

Closed dressing technique also proved beneficial in a recent clinical study by Luo et al.[34] 24 Chinese participants underwent FxCR to bilateral cheeks with identical laser settings. The left cheek had a mask composed of antimicrobial peptides (AMPs) and hyaluronic acid (HA) applied for 20 minutes postprocedure, while the right cheek was untreated. Erythema index and melanin index on the mask-treated side were statistically significantly lower at follow up appointments. On day 1, mask treated skin had lower TEWL than untreated skin indicating a more rapid wound reepithelization.[34] It is postulated that the combination of AMPs and HA accelerated wound healing. Antimicrobial peptides play a vital role in the innate immune system by downregulating the destructive inflammatory response, while upregulating antimicrobial immunity.[34] Hyaluronic acid, an important macromolecule in the ECM, increases in concentration in natural wound repair. This mucopolysaccharide provides a temporary wound structural foundation, allowing improved nutrient diffusion, waste removal, retention of moisture, and indirectly assisting in keratinocyte division and proliferation.[34,35]

While closed dressings appear to offer promise for laser-induced epidermal breakdown, further clinical experience is needed.

CONCLUSION

Laser ablation can yield incredible aesthetic results but remains a procedure with significant downtime. Despite technological advances and fractionated devices, patients still experience erythema, edema, crusting, exudate, and the risks of pigmentary changes, secondary infections and scarring.[22] A post-operative skincare regimen is critical to improve wound healing and reepithelization, and minimize patient discomfort and adverse effects. Standard post treatment care has involved open dressings with distilled water or acetic acid soaks and petroleum-based ointments. Newer topical agents and occlusive dressings now exist in the market to streamline and expedite wound repair and contain a variety of growth factors, stem cells, silicone bases, botanical active ingredients, and other anti-inflammatory agents. The clinical studies on these agents often contain small numbers of participants, vary in type, strength, and clinical indication of the resurfacing laser used, and have differing postprocedure evaluation protocols and assessments. Ultimately, the optimal choice of the postprocedural skincare plan will depend on each unique clinical scenario. As expedited healing is fundamental to clinical outcomes and patient satisfaction, further research is warranted to identify the optimal laser resurfacing skincare regimen.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Margot Chima MD

E-mail:..... Margotchima@gmail.com

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ORIGINAL ARTICLE

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Grover Disease Associated With Chemotherapy: Review of Potential Pathophysiology, Current Treatments, and Future Directions

Jacob Beer BA,[a] Misha Rosenbach MD[b]

[a]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[b]Department of Dermatology, University of Pennsylvania, Philadelphia, PA

ABSTRACT

Introduction: Transient acantholytic dermatosis has been frequently reported in patients with malignancies. While paraneoplastic cases have rarely been reported, most eruptions occur in the setting of chemotherapeutic agents. Management is based on limited data and primarily with topical steroids and topical emollients. A subset of patients exhibits recalcitrant disease and require alternate therapeutic approaches

Methods: This systematic review consisted of identifying records in PubMed using the medical subject headings (MeSH) terms "chemotherapy" AND "Grover", "chemotherapy" AND "Grover's", "cancer" AND "Grover", "cancer" AND "Grover's", "malignancy" AND "Grover", "malignancy" AND "Grover's", as well as a free text search for "Grover" OR "Grover's" OR "Grover disease" OR "Grovers disease" OR "Grover's disease" OR "transient acantholytic dermatosis" OR "transient acantholytic" to identify case reports, case series, systematic reviews, review articles, meta-analyses, clinical trials, brief commentaries, and original articles. The titles and abstracts of all results were reviewed. Full texts of relevant results were then read in their entirety and applicability was determined.

Results: Overall, Grover disease has rarely been reported in the setting of malignancy. When it occurs, it is generally in the setting of chemotherapy use. Chemotherapy-associated Grover disease is reported most frequently in association with cytotoxic chemotherapies, followed by small molecule inhibitors. The first line treatment for this complication is the use of topical agents. When these provide inadequate relief, alternate therapies have been rarely reported, with novel treatments proposed based on the type of chemotherapy agent and its mechanism of action.

Conclusions: Chemotherapy-associated Grover disease is an uncommon complication of cancer treatment. While most cases of chemotherapy-associated Grover disease can be treated with topical steroids and topical emollients, certain cases require a more specialized approach. This could include adjuvant adjuvant therapies, or novel treatments that are directly related to the mechanism of action of the chemotherapy involved.

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INTRODUCTION

History of Transient Acantholytic Dermatosis (Grover Disease)

Transient acantholytic dermatosis, or Grover disease, is a rare acantholytic skin disorder that was first described by Dr. Ralph Weir Grover.[1] Over the course of five years, he observed six patients who presented with unusual transient truncal rashes. In 1970, he published a case series of these six patients and observed that the histology indicated an acantholytic process that seemed consistent with Hailey-Hailey disease or Darier disease. However, the clinical presentations, including the age of onset, temporal transience, and distribution of lesions, were not consistent with either entity. As such, he termed the disease "transient acantholytic dermatosis" in order to note the transient nature of this acantholytic eruption. Over time, more patients were described as having a similar condition.[2-7] In many cases, their eruptions were not transient, prompting a shift toward the name "Grover's disease" initially, and with a shift in medical literature away from possessive, eponymous disease names, it is more commonly known as "Grover disease" or "transient acantholytic dermatosis," often used interchangeably.[8] The disease was later categorized by subtypes based on histological patterns, with four main subtypes: Hailey-Hailey-like, Darier-like, Pemphigus vulgaris-like, and Spongiotic.[9] Chalet et al described histopathological diagnosis principles that remain relevant in the diagnosis of Grover disease, despite changing clinical criteria (Table 1).[9] They note a clinical picture that consists of discrete lesions that do not demonstrate confluence and that can range from papulovesicular to keratotic. The lesions are frequently pruritic, and the primary locations include the upper chest, lumbar area, or the back. Although previously disputed, the consensus from the available literature is that Grover disease is more commonly diagnosed in the winter than in the summer.[8,10-12] Scheinfeld et al found a 4-fold increase of Grover disease diagnosis in winter months (January–March) than in summer months (June–August).[10] Grover disease is typically diagnosed in older, male patients with a mean age of 61 years when diagnosed and a male to female ratio of 2.4:1.[4,13,14]

TABLE 1.

Histopathological Diagnostic Guidelines for Grover Disease Adapted from Chalet et al[9]	
Histology	
Epidermis changes	• Acantholysis is the characteristic hallmark - Dyskeratosis typically seen - "corps ronds" and "grains" may be seen • Four Histologic Patterns 1. Darier-like a. Dyskeratotic and acantholytic cells in every epidermal layer b. Parakeratosis c. Cornified layer occasionally normal basket-weave configuration 2. Pemphigus vulgaris-like a. Focal suprabasal clefts 3. Hailey-Hailey-like a. Suprabasal clefts with acantholysis through the spinous layer b. Acantholysis could be seen only in the upper portion of the epidermis 4. Spongiotic a. Acantholysis in the spongiotic foci b. Intracellular edema is often present • > 2 of these patterns could be found in the same specimen
Dermis changes	• Lymphohistiocytic infiltrate in the vessels of the superficial plexus • Eosinophils may be present in the infiltrate. Their presence may be associated with spongiosis.

Discussion of Pathophysiology and Immunology

The exact pathogenesis of Grover disease is not entirely known. One theory suggests occlusion of the eccrine ducts leads to leakage, or "internal sweating."[13] This process in which sweat molecules leak from the ducts to the epidermis is proposed to lead to epidermal acantholysis. This is reinforced by Grover disease's association with increased sweating,[15] and further supported by the facts that sunlight and exercise exacerbate Grover disease in many patients, though other studies have failed to reproduce symptoms using light.[16,17] Notably, however, arguing against this theory, is the observation of an increased prevalence in the winter as opposed to summer months.[10] Some authors postulate that xerosis during winter months can be a trigger for Grover disease.[16] Histologically, areas of acantholysis have been shown with fluorescence to contain dissolved desmosomal plaque proteins, which is hypothesized to be from proteolytic sweat enzymes.[18] Furthermore, immunohistochemistry studies have failed to show a distinct relationship between the areas of acantholysis and eccrine duct function.[13,19] Finally, Weaver et al note that while the eccrine apparatus is likely involved, that Grover disease largely spares the palms and soles, areas rife with eccrine glands, suggesting that while eccrine gland involvement may be a characteristic of the disease, abnormalities at these glands are unlikely to completely explain the pathophysiology of Grover disease.[13]

A number of conditions have been associated with Grover disease.[11] Early retrospective studies by Grover et al found that individuals were more likely to be diagnosed with transient acantholytic dermatosis if they were diagnosed with other dermatologic conditions: asteatotic eczema, contact dermatitis, and acne rosacea.[11] The authors noted that therapies, such as emollient oils and cortisone, that were directed toward reducing inflammation and irritation of the underlying pathology proved useful in treating symptomatic Grover disease. Grover disease has been specifically associated with atopy, for which topical steroids were used to treat both atopic symptoms and those of Grover disease.[20] In several refractory cases of Grover disease that did not respond to typical treatments, patients were found to have infections, such as scabies and tinea versicolor, requiring treatment of their infections for the resolution of symptoms.[21-23] Upon starting hemodialysis, a subset of patients with chronic renal failure develop Grover disease that proves to be particularly refractory to standard treatments, with resolution occurring spontaneously occasionally only after extended periods of time or with renal transplantation.[24] It has been hypothesized that Grover disease is associated with conditions that affect the integrity of the epidermis (eg, renal disease, atopic dermatitis, skin infections), and that conditions that weaken this integrity can lead to Grover disease.[16]

The notion of Grover disease being an autoimmune dermatosis has been proposed, with anti-desmoglein antibodies found occasionally in patients with the disease.[25] However, it is more likely that these antibodies are non-pathogenic, and may arise from desmosomal disintegration or as a consequence of Grover disease-associated acantholysis exposing desmosomal proteins to the immune system and epitope spreading. Studies analyzing direct and indirect immunofluorescence in Grover disease are largely negative, with occasional studies demonstrating deposits of IgM and IgA, as well as C3 and fibrin.[17,26]

Histology

The histology seen in Grover disease demonstrates characteristic acantholysis, usually with dyskeratosis, similar to that seen in other disorders such as Darier disease and isolated

benign warty dyskeratomas. Several different patterns have been described over the years that can occur separately or in combination with other patterns. There are four main patterns of histology seen in patients with Grover disease: Darier-like pattern, Hailey-Hailey-like pattern, pemphigus vulgaris-like pattern, and the spongiotic-like pattern.[4,9] Other histologic findings have been noted, including a lichenoid pattern, a vesicular pattern, and a lentiginous pattern, though these and other rare features are less well-categorized.[10] The relative frequencies of different histologic variants remains unclear.[13,27] Some have suggested that the different patterns may indicate at which level the acantholysis is occurring, though this has not been demonstrated in large studies.[9,27] Alternatively, the different patterns may reflect differing etiologies.

The Darier-like pattern typically demonstrates focal acantholysis occurring at the suprabasal level, with dyskeratosis and parakeratosis occurring above in the epidermis.[9] Histology from this variant demonstrates round dyskeratotic keratinocytes (corps ronds) and compressed cells in the stratum corneum and granular layer with elongated nuclei (grains), similar to findings in Darier disease.[28] Conventional Darier disease is due to dysfunction of the sarco/endoplasmic reticulum Ca^{2+} ATPase pump (SERCA2) caused by a gene mutation.[29] Sakuntabhai et al. note that SERCA2 plays a pivotal role in the integrity of the epidermis by allowing adhesion between keratinocytes as well as enabling epithelial cell differentiation. This assumption is reinforced by the finding that increases in extracellular Ca^{2+} are needed for desmosome assembly[30] and that when selective SERCA inhibitors are employed, epithelial cells develop malformed intercellular junctions.[31] It has also been noted that mutation of this gene leads to impaired assembly of desmosomal proteins as well as to defective keratin expression, ultimately leading to dyskeratosis.[32] Using electron microscopy, many of the changes noted in Darier disease have been observed in Grover disease, indicating a potential overlap in treatments for both Darier disease and Grover disease with Darier-like pattern.[33] These treatments include systemic and topical retinoids.[34] Adapting other therapies that are potentially efficacious in treating Darier disease, such as recently-reported low-dose naltrexone,[34] may be another approach to treating recalcitrant Grover disease.

The Hailey-Hailey-like histologic pattern involves most layers of the epidermis, with some suprabasal clefting. Of note, the suprabasal acantholysis without associated dyskeratosis leads to the "dilapidated brick wall appearance" associated with this particular pattern, as seen in Hailey-Hailey.[13] Hailey-Hailey disease is due to a mutation in the gene ATP2C1, leading to the dysfunction of the ATP-powered, magnesium-dependent, calcium pump protein hsPCA1.[35] As described with Darier disease, the dysregulation of Ca^{2+} is believed to lead to the acantholysis and histologic manifestations of Hailey-Hailey disease, and may potentially play a role in the pathophysiology of some cases of Grover disease.

The pemphigus vulgaris pattern similarly tends to include suprabasal lesions, usually with little to no dyskeratosis. On histology, this pattern demonstrates a "tombstone" appearance arising from acantholysis of basal keratinocytes attached to the basement membrane.[12] This histology is typically associated with pemphigus vulgaris and, in that disease, is due to the IgG pemphigus autoantibody against desmoglein 1 and 3. In immunofluorescence studies of Grover disease, anti-desmoglein fluorescence has been shown to rarely demonstrate a staining pattern of peripheral pattern and chain of dots, similar to that of Hailey-Hailey disease if IF is performed and positive, and in contrast to the typical staining pattern of pemphigus vulgaris.[18]

The spongiotic-like pattern demonstrates with epidermal edema that leads to acantholysis. This occurs due to keratinocyte separation and breakdown of intracellular bridges.[13] This histologic pattern is more similar to that seen in eczematous dermatoses, and these findings are less specific for Grover disease.

In reviewing the histology of Grover disease, it is important to mention warty dyskeratomas. These tend to present as isolated erythematous papular lesions that occur most commonly on the head and neck. The underlying histology has been noted to resemble the epidermal reaction pattern of Grover disease and Darier disease.[36] This includes suprabasilar acantholysis containing dyskeratotic keratinocytes, and can include a stellate scale crust that can be found in Darier disease and Grover disease.[36] Further study of these various entities which display similar, overlapping histologic features, may help elucidate the pathophysiology of the distinctive pattern of acantholysis seen in these diseases.

Chemotherapy-Associated Grover Disease

While not a paraneoplastic entity, Grover disease has occasionally been noted in the presence of malignancy.[12,37,38] Development of transient acantholytic dermatosis has been reported in isolated case reports in conjunction with a variety malignancies: gastric carcinoma,[39] carcinoid tumor of the thymus,[40] leukemia cutis,[41] multiple myeloma,[42] and acute myeloid leukemia.[43] In these cases, Grover disease was felt by reporting authors to be associated with the malignant process involved, as opposed to the initiation of any intervention. Given the rarity of Grover disease in the setting of malignancy, a true paraneoplastic relationship is unlikely. It is more likely that idiopathic Grover disease is not uncommon, and some patients with Grover also develop malignancy, with their skin disease being noted or reported for the first time in the setting of their cancer treatment. A prospective analysis of hospitalized patients failed to find a relationship between malignancy and Grover disease, further supporting the idea that Grover disease is not truly paraneoplastic.[14]

TABLE 2.

Chemotherapy Agents Associated With Grover Disease			
Chemotherapy Classification	**Literature**	**Agents involved**	**Management**
Cytotoxic Agents			
	Horn et al[37](1987)	Carmustine Cyclophosphamide Etoposide Cisplatin Cytarabine Daunorubicin	• Spontaneous resolution
	Guana et al[61] (1994)	Methotrexate Vinblastine Platinum Carboplatin Doxorubicin Cyclophosphamide	• Lactic acid lotion • Topical corticosteroids • Antihistamine
	Cohen et al[63] (1997)	2-chlorodeoxyadenosine	• Topical corticosteroids
	Harvell et al[62] (1998)	Etoposide Cyclophosphamide Carboplatin Busulfan	• Topical corticosteroids • Spontaneous resolution • Chlorhexidine gluconate washes
	Cohen et al[64] (1999)	2-chlorodeoxyadenosine	• Topical corticosteroids
	Bolaños-Meade et al[65] (2007)	Fludarabine Cyclophosphamide	• Cessation of cytotoxic agent
	Villalon et al[44] (2007)	Idarubicine Etoposide Cytarabine	• Spontaneous resolution (with recurrence)
	Ippoliti et al[66] (2012)	Cyclophosphamide Vincristine Adriblastine	• Spontaneous resolution
	Butler et al[87] (2014)	Panabinostat Cytarabine Daunorubicin Busulfan Fludarabine	• None mentioned
	Lim et al[67] (2016)	Busulfan Cyclophosphamide	• Cessation of cytotoxic agent
	Auh et al[48] (2017)	Daunorubicin Cytarabine	• None mentioned
	Khan et al6[8] (2020)	Carboplatin-pemetrexed[1]	• Topical corticosteroids
Small Molecule Inhibitors			
BRAF Inhibitors			
	Anforth et al[88] (2012)	Dabrafenib	• None mentioned
	Gupta et al[89] (2012)	Vemurafenib	• None mentioned
	Chu et al[57] (2012)	Vemurafenib Dabrafenib	• Topical corticosteroids • Medication dose reduction
	Sabatier-Vincent et al[75] (2014)	Vemurafenib	• Topical emollients

TABLE 2.

Chemotherapy Agents Associated With Grover Disease			
Chemotherapy Classification	**Literature**	**Agents involved**	**Management**
	Carlos et al[56] (2015)	Vemurafenib Dabrafenib	• Topical emollients • Topical corticosteroids • Oral corticosteroids • Oral acitretin
	Anforth et al[90] (2015)	Vemurafenib Dabrafenib	• None mentioned
	Singh et al[76] (2020)	Vemurafenib	• Topical emollients • Topical corticosteroids
Immune Checkpoint Inhibitors			
	Munoz et al[74] (2014)	Ipilimumab Dacarbazine	• Moisturizing cream • Antihistamines
	Uemura et al[54] (2016)	Ipilimumab	• Antihistamines • Topical corticosteroids (minimal improvement)
	Koelzer et al[53] (2016)	Ipilimumab	• Topical corticosteroids (relieved symptoms but rash persisted)
	Kaunitz et al[73] (2017)	Anti-PD-1 agents[2] Anti-CTLA-4 agents[3]	• Medication cessation • Systemic corticosteroids
	Perret et al[71] (2017)	Ipilimumab Nivolumab Pembrolizumab	• Medication cessation • Systemic corticosteroids • Antihistamines • Moisturizing cream • Topical corticosteroids • Topical emollients
	Chen et al[72] (2018)	Pembrolizumab[4] Ipilimumab	• Medication cessation • Systemic corticosteroids • Topical corticosteroids • Antihistamine
Other Small Molecule Inhibitors			
	Tscharner et al[51] (2006)	Cetuximab[5]	• Medication cessation • Halometasone cream with triclosan • Topical emollients

[1]Pembrolizumab was also used, however, patient presented after use of carboplatin-pemetrexed.
[2]Unspecified
[3]Unspecified
[4]Fluorouracil, cisplatin, docetaxel, carboplatin, cetuximab, and paclitaxel were also used at various points, however, patients presented shortly after initiation of pembrolizumab and/or ipilimumab.
[5]Fluorouracil and oxaliplatin were also used, however, patient presented shortly after initiation of cetuximab.

Notably, however, Grover disease has been observed to develop shortly after chemotherapy induction.[44,45] This has been reported following the initiation of cytotoxic agents (in particular cyclophosphamide) and small molecule inhibitors (most notably B-Rapidly Accelerated Fibrosarcoma (BRAF) inhibitors as well as immune checkpoint inhibitors) (Table 2).

Cytotoxic chemotherapeutic agents have the most commonly reported association with transient acantholytic dermatosis. While the underlying mechanism is not entirely known, the prevailing theory is that these agents concentrate in the eccrine glands and are excreted in the epidermis, creating directly toxic effects at the epidermis, causing dyskeratosis and acantholysis.[46] Additionally, cytotoxic chemotherapies, notably cytarabine, have been associated with toxic erythema of chemotherapy, which tends to involve the hands and feet (sites of high concentrations of eccrine coils), and with neutrophilic eccrine hidradenitis (NEH).[47] The proposed mechanism in this pathology is that the direct toxicity of these agents causes cell death that releases toxic byproducts and recruits neutrophils.[47] NEH and transient acantholytic dermatosis have not been described concurrently to date, however, the established connection between eccrine gland damage from cytotoxic agents that is seen in NEH may parallel similar damage at other sites leading to Grover disease. Both NEH and Grover disease have been reported in association with cytarabine.[37,44,48] Cases of transient acantholytic dermatosis have been most commonly reported shortly after the induction of alkylating agents, compared with other cytotoxic agents. This may be due to the increased rate of xerosis following induction of alkylating agent chemotherapy.[49] Cytotoxic chemotherapeutic agents, particularly alkylating agents, inhibit proliferation among keratinocytes, ultimately leading to xerosis.[50] The xerosis associated with these agents could trigger the eruption that is seen in Grover disease, in a fashion similar to xerosis produced during winter months.

While most reports of cytotoxic chemotherapy-associated Grover disease have been in isolated case reports and case series, there are emerging reports of Grover disease in the setting of targeted, small-molecule inhibitors. One of the first small molecule inhibitors implicated in the development of Grover disease was cetuximab, an epidermal growth factor (EGF) receptor antagonist.[51] EGF receptor antagonists diminish proliferation of keratinocytes and increase their expression of inflammatory chemokines.[52] These changes can lead to xerosis, particularly in elderly patients, as well as a striking acneiform folliculitis.[52] Additional small-molecule inhibitors have been reported in association with Grover disease as well, as shown in Table 2. Chemotherapy-associated transient acantholytic dermatosis has been reported with increasing frequency in the setting of Immune checkpoint inhibitor therapy. While these agents can also induce xerosis, the broad immune stimulation associated with checkpoint inhibitors may induce decreased immune tolerance to normal skin, contributing to TAD.[53] Notably this eruption may be drug-, rather than class-, specific, as in one case report, ipilimumab induced the eruption of Grover disease, whereas anti-PD1 therapy did not.[54] This corresponds with the higher prevalence of reported cases associated with ipilimumab, as opposed to other immune checkpoint inhibitors. Immunohistochemistry analysis in patients on ipilimumab found elevated GATA-binding protein 3, a Th2 transcription factor. This may suggest that ipilimumab-induced Grover disease is due to Th2 cells, which coincides with previous associations of IL-4 with Grover disease.[54,55]

BRAF inhibitors have been reported to induce transient acantholytic dermatosis, but notably BRAF inhibitors are also known to induce multiple warty dyskeratoma-like lesions, which may make identification of true BRAF-inhibitor-associated TAD more challenging, but which further supports the concept of overlap between those two entities when they occur idiopathically as well. In evaluating patients taking the BRAF inhibitors vemurafenib and dabrafenib, Carlos et al note that the most common cutaneous adverse effect seen was Grover disease.[56] Chu et al note that many of the patients treated with the BRAF inhibitor vemurafenib developed TAD-like eruptions and/or warty dyskeratomas.[57] One theory for the pathogenesis in this setting is that the onset of Grover disease following BRAF monotherapy arises from paradoxical activation of mitogen-activated protein kinase (MAPK), which leads to keratinocyte proliferation that progresses to acantholysis. In the epidermis, proteins involved in the ERK-MAPK signaling pathway are maintained by a spatial gradient in proportion to calcium signaling.[58] Interruption of this pathway, such as from a BRAF inhibitor, may result in lesions that are similar to those seen in disorders of calcium transport, such as Darier disease. Another theory is that BRAF inhibitors cause a direct off-site effect, leading to acantholysis.[59] In analyzing BRAF in the presence of RAS leading to tumorigenesis, authors have proposed that inhibition of BRAF allows BRAF to bind CRAF through a RAS-dependent process. This in turn, activates CRAF and MEK-ERK signaling, which leads to hyperkeratosis that may produce acantholysis. It has been reported that when MEK inhibitors are added to BRAF inhibitor therapy, that Grover disease fails to develop.[60] As combination therapy has become more standard, TAD-like eruptions may be observed less frequently, and patients with cutaneous adverse effects on BRAF-inhibitor monotherapy may potentially improve with the addition of MEK combination therapy.

Therapeutic Approach

Reported Treatments in Chemotherapy Associated Cases

To date, no randomized, placebo-controlled studies have examined therapies for Grover disease, particularly in chemotherapy-associated cases. As a result, the majority of current treatments derive from published case series and case reports, which have an inherent bias and lack numerator and denominator data or prospective evaluation with which to demonstrate efficacy. Additionally, the efficacy of treatments is difficult to measure due to the lack of a unified case definition, the variable severity and duration of symptoms, and the potential for spontaneous remission. When there are clear triggers for symptoms, such as sweating and heat, management involves avoiding these triggers. Current therapies for Grover disease largely revolve around symptomatic management as shown in Table 2. Within the context of chemotherapy-associated Grover disease, different treatments have been implemented depending on the severity of symptoms as well as the category of chemotherapy agent used.

In patients who are on a cytotoxic chemotherapy regimen, reported treatments for Grover disease are limited to varied single case reports.[37,44,61-68] Many patients who endorse mild symptoms on these regimens experience spontaneous resolution on their symptoms after completion of therapy.[37,66] Some patients with mild symptoms experienced spontaneous resolution with recurrence upon re-initiation of their cytotoxic therapies.[44] In the majority of patients on cytotoxic chemotherapy treatments, application of topical corticosteroids sufficiently ameliorated their symptoms.[61-64,68] Topical corticosteroids have historically been one of the mainstays of treatment in patients with idiopathic Grover disease, as they tend to alleviate inflammation and pruritus.[69,70] Adjuvant therapies used in certain patients were chlorhexidine gluconate washes, antihistamines, and lactic acid lotion.[61,62] In certain cases, symptoms did not resolve until cessation of the cytotoxic agent.[65,67]

For patients who develop Grover disease shortly after the initiation of immune checkpoint inhibitors, the majority of existing reports note use of corticosteroids.[53,54,71-73] Perret et al and Koelzer et al noted that in several patients on ipilimumab, systemic corticosteroids were required, as their symptoms were refractory to topical corticosteroids.[53,71] Munoz et al note the remission of symptoms without treatment after completion

of the patient's course of immunotherapy.[74] Kaunitz et al noted that while the majority of patients studied were able to maintain their immunotherapy while using topical corticosteroids, several required the cessation of their treatments and the use of systemic corticosteroids for symptoms of Grover disease as well as other adverse effects.[73] The hypothesis that Grover disease is associated with increased Th2 production and infiltration, especially in cases related to ipilimumab, indicate that a targeted Th2 disruption or IL4 monoclonal antibody may be more effective than a general immune system suppression, though data is lacking.[54,55] For other small molecule inhibitors, cetuximab induced Grover disease symptoms abated upon the use of topical corticosteroids and topical emollients, and the eventual cessation of the medication.[51]

Cases of Grover disease associated with BRAF inhibitors have largely been treated with topical emollients or topical corticosteroids.[56,57,75,76] In certain cases, the dose was decreased in order to ameliorate side effects experienced, which included symptomatic Grover disease.[57] Oral acitretin has been used as an adjuvant treatment.[56] Given the addition of MEK inhibitors decrease the cutaneous adverse effects of patients on BRAF inhibitor monotherapy, patients receiving BRAF inhibitors who develop Grover disease may benefit from a dermatologic standpoint by the addition of a MEK inhibitor.[56] In most cases, Grover disease can be managed with supportive care, such as topical steroids and emollients, however, it is important to recognize that combination therapy may avoid or improve this skin side effect. Furthermore, this may elucidate the mechanism of both chemotherapy-associated Grover disease as well as potentially idiopathic Grover disease.

Topical corticosteroids and emollients are the most commonly used management of chemotherapy-associated Grover disease. While this approach appears effective in the majority of cases, some patients develop severe symptoms, leading to dose reduction or alteration of the chemotherapy regimen.[44,51,54,57,65,67] Occasionally, oral corticosteroids required for relief.[56] From these cases, it becomes clear that a more personalized approach is needed to treat these patients with refractory symptoms on chemotherapy regimens.

Potential Treatments in Chemotherapy Associated Cases

For patients with idiopathic Grover disease that is refractory to traditional first line treatments, additional therapies have been used with variable success in isolated case reports or small case series. In the field of supportive oncodermatology, it is essential to balance the management of the cutaneous adverse event in the context of the patient's overall clinical course. Management of the underlying malignancy is paramount, and it is important that any therapy under consideration for the skin does not interfere with the optimal approach to managing the malignancy. As always, it is important to balance patient comorbidities with the efficacy, safety, side effect profile, and cost of the dermatologic treatment under consideration.

While infrequently used in patients with chemotherapy-associated Grover disease, oral retinoids have been shown to be helpful in a limited number of patients with idiopathic Grover disease.[56] In a patient with persistent, recalcitrant Grover disease with no obvious triggers, 6 weeks of oral acitretin resulted in complete remission without reported recurrence.[77] By examining patients with more resistant idiopathic Grover disease, it was found that oral isotretinoin was effective for up to 10 months of remission.[78] This could be particularly beneficial to patients who develop Grover disease with one chemotherapeutic agent but require multiple rounds of treatment with that drug. Topical vitamin D analogues have also been found to be beneficial in the treatment of Grover disease, particularly in patients who exhibit the Darier-like histologic pattern.[77,79] As Darier disease is due to a dysfunction in the SERCA calcium channel, the addition of a vitamin D analogue could allow for regulation of calcium in the epidermis through opening alternative calcium channels.[80] Additionally, the role of vitamin D in the suppression of keratinocyte proliferation in sebaceous glands could be beneficial in Grover disease by decreasing or preventing occlusion of the glands.[79] While the combination of oral retinoids and topical vitamin D has also been found to be effective in the treatment of pruritus associated with Grover disease, the data on this combination is limited.[78]

In recalcitrant or complicated cases of idiopathic Grover disease, phototherapy and photodynamic therapy have proven effective.[81-85] Specifically, narrowband ultraviolet B phototherapy as well as psoralen plus ultraviolet A photochemotherapy have been found to be effective in treating patients' idiopathic Grover disease.[81] Red-light 5-am-inolevulinic acid photodynamic therapy (ALA-PDT) was successfully used to treat a patient with refractory symptoms that were presumably caused by heat and sweating.[82] The proposed mechanism is that ALA accumulates in the irregular epidermis that is then destroyed by photodynamic therapy. In patients who failed topical and systemic steroid treatment, UVB and photodynamic therapy, total electron beam radiotherapy was shown to be successful in alleviating the patient's symptoms, but represents a radical approach which is beyond what is required in most cases.[86] Phototherapy may be a helpful alternative option in patients with recalcitrant chemotherapy-associated cases, as a non-immunosuppressive, well-tolerated treatment option, though availability may vary by site and whether patients undergoing cancer treatment are inpatients or outpatients

CONCLUSION

Grover disease is a rare inflammatory disease with pruritic papules on the trunk and a distinctive histologic pattern, which may represent a disorder of sweating or the eccrine coils, with or without a host inflammatory response. While idiopathic Grover disease is uncommon, it can also develop in the setting

of malignancy – not primarily as a paraneoplastic eruption, but may occur instead in the setting of chemotherapy, both with broadly cytotoxic chemotherapy and with emerging reports of TAD in association with small molecule inhibitors. Some of these eruptions may be due to the targeted pathway, as in BRAF or EGFR inhibitors, or due to immune stimulation, as with checkpoint inhibitors.

Chemotherapy-associated cases of Grover disease have mainly been managed with topical steroids and topical emollients, with resolution of symptoms. In severe cases, the chemotherapy regimen may be altered, or the patient may begin oral steroids, complicating the patient's clinical course. For these cases it is important to determine alternative treatments that can be used for the symptoms of Grover disease. These adjuvant treatments may be ones that have been successful in idiopathic Grover disease or may be ones that are specific to the chemotherapy agent used. Further research employing these regimens is needed to determine the efficacy of such treatments as well as the practicality.

DISCLOSURES

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AUTHOR CORRESPONDENCE

Jacob Beer
E-mail:..... jacob.beer@pennmedicine.upenn.edu

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Sequential Treatment of Actinic Keratosis and Photoaging by Daylight PDT and Injectable NASHA Gel as Skin Booster

Magda Belmontesi MD
Studio Medico Belmontesi, Vigevano, Italy

ABSTRACT

Introduction: Actinic keratosis (AK) is a common intraepithelial atypical proliferation of keratinocytes that might progress into invasive squamous cell carcinoma.

Method: We have tested the treatment using sequential sessions of photodynamic therapy in daylight and injectable non-animal hyaluronic acid gel skin boosters (NSBs) on 4 patients with AK on head and neck. Two further sessions of NSBs were scheduled, 30 and 60 days after the first injection, to improve the overall skin quality.

Results: All patients showed a clinically significant improvement of the overall face skin quality, photoaging signs, and fine wrinkles; all patients were satisfied of the treatment outcome. None of the patients reported any side effect related to the treatment.

Discussion: The combination of two minimally invasive treatments showed to be effective giving the almost complete resolution of AK and a clear improvement of skin texture, with noticeable reduction of the clinical signs of skin photoaging, meeting patient's expectations.

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INTRODUCTION

Actinic keratosis (AK) is a common intraepithelial atypical proliferation of keratinocytes that clinically develop as small slow-growing scaly or keratotic erythematous patches or papules on chronically sun-exposed areas.[1,2]

The overall world AK prevalence is 6%–60%, depending on age, gender, predisposing risk factors, and geographical location.[2] In Italy, AK prevalence in 7,282 dermatology outpatients has been estimated at 27.4% (34.3% in men and 20.0% in women) with an increase after 40–50 years.[3]

Clinical severity of individual AKs is commonly assessed according to the Olsen classification system based on AK overall thickness, from Grade 1 (slight palpability) to Grade 2 (moderately thick), and Grade 3 (very thick).[4]

Regardless of the clinical grade, AK may progress into invasive squamous cell carcinoma (SCC), although the progression rate of AK to SCC is not clearly known and difficult to ascertain.[4,5]

Sun-exposed skin areas surrounding AKs show subclinical alterations, in terms of gene expression and early molecular and histological changes, similar to those found in AKs. These sun-damaged skin areas are prone to the development of further AK lesions and sun-related skin cancers and are known as field cancerization.[6]

Due to the lack of prognostic tools to identify individual lesions at risk of progression to invasive SCC, guidelines recommend treating each AK lesion.[7] Field-directed treatment is also recommended when more than 5 AKs are present in the field.[4]

Patients with AKs may complain the overall cosmetic burden of their condition, and today, more and more patients with AKs seek for a concomitant improvement of the visible photoaging signs around the AKs, represented by thicker skin texture, yellow discoloration, dyschromia, coarse wrinkles, telangiectasias, erythema, and sagging skin.[8] Therefore, current therapeutic approach to treat AKs and field cancerization may include complementary strategies to improve the overall cosmetic appearance.

CASE PRESENTATION

Four patients with multiple AKs (mostly grade 1) and moderate to severe photoaging on face and/or scalp were treated at our clinic, according to an approach based on sequential sessions of photodynamic therapy (PDT) in daylight (DL) to treat AKs and the field cancerization, and injectable non-animal stabilized hyaluronic acid (NASHA®) gel skin boosters (NSBs) to improve the overall skin quality. Patients' demographic and clinical characteristics are summarized in Table 1.

TABLE 1.

Patients' Characteristics	
Patients	2 males, 2 females
Mean age	64 years (range, 62–67 years)
AK severity assessment	Grade 1-2 (Olsen Classification)
AK number	Range: 11–18
AK location	Face, scalp
Photoaging severity assessment	Moderate to severe (Glogau Classification)

TABLE 2.

Treatment Protocol Based on Sequential Sessions of Daylight PDT and NSBS	
First visit – Clinical assessment	Information to patient, treatment plan and instructions on skin preparation, at home, to be started 15 days before the scheduled Daylight-PDT session
Day 30 – DayLight-PDT (1° session)	Inside the clinic: (20 minutes): sunscreen, curettage, MAL application (no occlusion required) Outdoor within 30 minutes after MAL application: 2 hours exposure to sunlight Inside the clinic: (5 minutes) MAL removal with water, assessment and post-treatment instructions
Day 60 – First NSBs injection	up to 2 ml on photodamaged skin of the face
Day 90 – Second NSBs injection	1 ml on photodamaged face skin
Day 120 –Third NSBs injection	1 ml on photodamaged face skin
Day 135 – Daylight-PDT (if required)	Only in case of incomplete AK response to the first Daylight session

FIGURES 1 AND 2. (Left) Actinic keratosis (AK) lesions in a female patient before daylight PDT–NSB sequential treatment. (Right) Improvement after daylight PDT and three NSB sessions.

FIGURES 3 AND 4. (Left) Actinic keratosis (AK) lesions in a male patient before daylight PDT–NSB sequential treatment. (Right) Improvement after daylight PDT and three NSB sessions.

At the baseline assessment during the first visit, patients were instructed to apply at home, daily, a 30% urea cream on the affected areas as keratolytic to prepare their skin for daylight-PDT. After 15 days they returned to the clinic to perform daylight PDT according to the following treatment modality: a 50+ SPF (Sun Protective Factor) chemical sunscreen was applied on all photo-exposed body areas; then, after curettage to remove scales and crusts, a cream containing Methyl-aminolevulinate 16mg/g (MAL) (Metvix/Metvixia, Galderma) was applied in a thin layer to the whole affected areas (individual AKs and field); after a time interval of 20–30 minutes, patients went outside and remained exposed to full daylight for two consecutive hours; then MAL was washed off and the patient was sent home. The patient was instructed to cover the treatment area for the rest of the day to reduce sun-related skin reactions. Use of gentle cleansers and moisturizers was also recommended for the following week.[9] 30 days after daylight PDT, a first session of NSBs (Restylane Skinboosters Vital; Q-MED AB/Galderma, Uppsala, Sweden) was carried out. Up to 2 ml of gel were injected on the photodamaged facial areas by multiple micro-punctures into the reticular dermis or sub-dermis.

The activation of the SmartClick™ system of the NSB syringe to release a dosed amount of gel for each depot (10µl) was the technique of choice.[10] Two further sessions of NSBs were scheduled, 30 days apart; during the second and the third session 1 ml of NSBs was injected. A second daylight PDT session was carried out in 2 patients due to incomplete AK response at the follow-up visit after about 4 months from the first PDT session (Table 2).

The patients were treated between June and October 2018. 30 days after daylight PDT, the total number of AKs (lesion count) decreased from a range of 11–18 to 0–4. The cosmetic result was very good with a global improvement of skin appearance.

After 3 sequential NSB sessions, overall face skin quality, in particular skin texture, photoaging signs, and fine wrinkles, showed a progressive improvement (Figures 1–4). All patients were satisfied of the treatment outcome. Only mild side effects (erythema, desquamation) were reported in the first week after daylight PDT.

DISCUSSION

PDT is recommended as a first-line treatment for individual (lesion-directed therapy) as well as for multiple and/or confluent AKs (field therapy) and has the potential to delay/reduce the development of new lesions.[4]

PDT is based upon the application of a photosensitizing agent (5-ALA, MAL), a prodrug which, when activated by illumination with a specific light source, is transformed into protoporphyrin IX (PpIX), inducing cytotoxic action, apoptosis, and selective necrosis of target cells. The absorption peaks of PpIX fall within the range of 400 to 700 nm (visible light).[11]

In conventional PDT (c-PDT), the cream containing the prodrug is applied for three hours to the affected site, then the lesions are exposed to red LED light (570–670 nm).

Methyl-aminolevulinate (MAL) cream has been approved in several countries using also daylight (MAL DL-PDT) to treat mild-to-moderate AK of face and scalp.[9,12]

In MAL-DL-PDT, patients expose to natural light within 30 minutes from MAL application and are required to stay outside for two hours. A structured expert consensus statement rated MAL DL-PDT as the preferred option for patients with multiple grade I or II AKs on both small and large cancerization fields due to its efficacy and tolerability profile.[9,13] Randomized controlled studies show non-inferiority of daylight-PDT compared to c-PDT in terms of efficacy with a better tolerability.[9] In particular, MAL-DL-PDT is associated to lower frequency and severity of side effects with almost absence of pain. Furthermore, high patient's and physician's satisfaction with the cosmetic appearance of the treated skin has been reported in a large observational study.[12]

In clinical practice, patients requiring therapy for AKs often seek for an improvement of the cutaneous appearance in terms of photoaging signs and skin texture. NASHA® has been one of the most extensively documented and commonly used gels for soft tissue augmentation over the last 20 years. NSBs are NASHA® gels specifically designed to progressively improve skin quality through intradermal or subdermal injection in very small aliquots. Recently, the first consensus on the use of NSBs was published. The authors strongly agreed on defining NSBs as a medical treatment for the skin with a double effect on texture appearance and skin structure with progressive and long-lasting effects.[10]

After 3 injection sessions, 1 per month, clinical effects of NSB on skin elasticity,[14] skin compactness,[15] hydration, wrinkles,[16] and acne scars[17] are reported; progressive and long-lasting improvements in skin quality seems to be related to collagen synthesis stimulation and dermal matrix components restoration. This stimulatory effect may be induced by mechanical stretching of the dermis, which in turn leads to stretching and activation of fibroblasts.[18]

NSBs have been associated with daylight PDT in a few series of patients; a combined sequential approach based on one session of daylight PDT followed by three monthly sessions of NSB, was used in patients with mild to moderate AKs, aiming to treat both AK lesions and peripheral cancerization field, and to improve skin quality. High AK response rate after PDT in daylight and a visible improvement of overall skin quality and fine wrinkling were observed. Both treatments were well tolerated with only mild expected side effects reported and well accepted by patients. Moreover, the proposed treatment meets the expectation of those people seeking a cosmetic improvement and therefore has the potential to increase patient's adherence to the follow-up visits for AKs. Randomized controlled studies are needed to demonstrate if a complementary or synergic action between the two treatments may explain the observed clinical improvement in these few cases and to confirm treatment efficacy.

CONCLUSION

The combination of two minimally invasive, effective and well-tolerated therapies characterized by excellent compliance allowed almost complete resolution of actinic keratosis and a clear improvement of skin texture, with noticeable reduction of the clinical signs of skin photoaging, meeting patient's expectations.

DISCLOSURES

Dr. Belmontesi has served as an advisor and lectures for Galderma Italy. No fee has been received for this article.

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AUTHOR CORRESPONDENCE

Magda Belmontesi MD
E-mail:..... studiobelmontesi@pelleedintorni.it

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ORIGINAL ARTICLE

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Choosing the Right Partner: Complementing Prescription Acne Medication With Over-the-Counter Cleansers and Moisturizers

Edward Lain MD FAAD,[a] Anneke E. Andriessen PhD[b]

[a]Sanova Dermatology, Austin TX; Austin Institute for Clinical Research, Austin, TX

[b]Radboud UMC Nijmegen, Andriessen Consultants, Malden, NL

ABSTRACT

Background: Acne is the most common dermatological disorder. An impaired barrier function in acne vulgaris has been reported, as well as decreased amounts of epidermal ceramides. Also, many of the systemic and topical medications prescribed for the treatment of acne exacerbate these skin barrier disruptions and can lead to irritation and dry skin conditions.

Aim: The review explored the importance of maximizing adjunctive skincare, such as over-the-counter products for managing acne and avoiding adverse effects.

Methods: A literature review was conducted and included clinical acne guidelines, clinical studies, and review articles on acne prevention, treatment, and maintenance. Searches were made in PubMed and Google Scholar for English-language literature published between Jan 1, 2010, and Apr 1, 2020. Two clinicians manually reviewed selected publications.

Results: Seventy-four articles were included in the analyses. A variety of specialized cleansers and moisturizers are available as suitable adjunctive therapies for acne-prone skin. Lipid-free cleansers were found to be the most appropriate type of cleanser for acne-prone skin as they were associated with a low risk of skin irritation, and a near-physiological stratum corneum pH. Moisturizers typically included ingredients such as humectants, emollients, oil absorbers, and those with anti-inflammatory and/or barrier replenishing properties. Given the various adjunctive products available, decision frameworks were created for clinicians to use when selecting over-the-counter cleansers and moisturizers for acne-prone patients.

Conclusion: Informing clinicians about skin barrier dysfunction in acne and the benefits of adjunctive skincare may help them to choose the right product(s) to complement prescription therapy.

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BACKGROUND

Acne is the most common dermatological disorder.[1] Psychological and emotional distress due to acne, including poor self-esteem, social anxiety, depression, and suicidal ideation have been reported in various studies.[2,3,4] Acne is a complex, multifactorial disease, and its pathophysiology is incompletely elucidated. An impaired barrier function in acne vulgaris has been reported, as well as decreased amounts of ceramides.[5]The structural and functional integrity of the stratum corneum is highly dependent on adequate hydration in the skin barrier. However, in acne-prone skin, barrier integrity is compromised both functionally (sebum excretion is higher, sebaceous glands are larger and subclinical inflammation is present) and via ultrastructural properties (filaggrin expression is enhanced, free fatty acids are reduced, linoleic acid, free sphingosine, and total ceramides are altered).[6]

Many of the systemic and topical medications prescribed for the treatment of acne, such as retinoids, antibiotics, and benzoyl peroxide, are associated with skin barrier alteration.[7] This, in turn, can cause irritation and dry skin conditions.[8] These unwanted effects can reduce adherence to treatment, and therapeutic outcomes.[8,9] Over-the-counter (OTC) non-comedogenic cleansers and moisturizers have been used successfully to reduce skin irritation.[9] However, some of these products, such as those with a high pH, have been shown to interfere with the efficacy of topical treatments for acne.[8] Managing the irritation potential of topical acne medications through the selective use of adjunctive, OTC skincare is an important strategy for improving treatment adherence and outcomes.

Aim of review

A literature review was conducted to explore clinical insights into skin barrier dysfunction in acne and the role of cleansing and moisturizers as adjunctive to prescription acne treatment. Informing health care providers about skin barrier dysfunction in acne and the benefits of adjunctive skincare may help them to choose the right OTC product(s) when complementing prescription therapy.

METHODS

The present literature review includes clinical acne guidelines, clinical studies, and review articles on acne prevention, treatment, and maintenance. Manuscripts focused on dermocosmetic regimens for acne were targeted. For this purpose, searches were made during two phases using PubMed and Google Scholar. The first phase was performed between July 10th and 12th, 2019, using search dates of Jan 1, 2010, to Jul 1, 2019; and the second phase occurred between April 6th and 8th 2020, using the search dates of Jul 2, 2019, to Apr 1, 2020. Searches were made for English-language literature using the following terms: *"Acne vulgaris, acne pathogenesis, skin microbiome and acne, acne exposome, acne therapy with OTC regimens, dermo-cosmetics, active cosmetics, sebostatics, keratinization, acne guidelines, algorithms for adult females with acne."* Exclusion criteria included: No original data (unless a review article was deemed relevant) and not dealing with the management of acne. Two clinicians manually reviewed the selected publications for additional resources.

RESULTS

After the exclusion of duplicates, the review yielded seventy-four papers deemed clinically relevant to adult female acne and the use of OTC regimens.[1-74] These seventy-four articles were used to formulate the below discussion.

DISCUSSION

Acne And Skin Barrier

Increased trans-epidermal-water-loss (TEWL) and inconsistent ceramide content in the stratum corneum are well characterized in acne patients, even in non-lesional skin.[5] Topical treatments for acne, including benzoyl peroxide, tazarotene, and tretinoin, have been proven to disrupt the skin barrier even further.[7] Improving skin barrier function is important for increasing tolerability, leading to enhanced adherence to treatment and, therefore, efficacy.[7] The primary goal of adjunctive skincare focuses on repairing the epidermal barrier in order to reduce TEWL, improve epidermal hydration, and ensure emollience. By sealing in water through occlusion, moisturizers may employ a hydrophobic barrier to water loss. Common ingredients capable of displaying this characteristic include petrolatum, lanolin, cetyl alcohol, ceramides, oils, and silicone/dimethicone. These ingredients have been proven to reduce TEWL by 20 to 98%.[75] Humectants, once incorrectly thought to attract water from the environment, draw hydration from the deeper dermis and epidermis into the stratum corneum. Examples of humectants used in moisturizers include glycerine, hyaluronic acid, vitamin E, sorbitol, sodium lactate, and urea. Ingredients such as cholesterol, squalene, fatty acids, and glycol stearate, fill the gaps between dead corneocytes and thereby smooth the skin surface. This provides an immediate effect of improved skin touch and texture, also known as emollience.

Ceramides are composed of a sphingosine base and a fatty acid and act synergistically on skin hydration and TEWL.[76] In the epidermis, ceramides constitute approximately 50% of the lipid composition of the stratum corneum. Cholesterol, fatty acids, and other lipids constitute approximately 25, 10, and 15%, respectively. Alterations in these ratios within the stratum corneum have been linked to several skin diseases, such as atopic dermatitis, acne, and rosacea, with the common them of impaired barrier function amongst them. Moisturizers can effectively repair barrier function by replacing the physiologic ratio of ceramides, cholesterol, and fatty acids. Particular ceramides used in topical skincare products include types 1, 3, 5, and 6-II. Ceramide 1 participates in cell signaling and thus orchestrates the ratio of the lipid composition of the stratum corneum. Ceramides 3, 5, and 6-II are in high concentration in the lipid bilayer, indicating their relative importance in maintaining the structural component of the stratum corneum as well as imparting essential barrier properties to the outer layer of the epidermis.[77]

Skincare Regimen in Acne Patients

Despite an increase in the sebum secretion rate associated with acne, Yamamoto et al, (1995) showed a reduction in sphingolipids (ceramides) in the stratum corneum.[5] Barrier dysfunction correlates with hyperkeratinization and comedone formation.[22] Therefore, an effective adjuvant skincare regimen must focus on the removal of excess sebum and debris on the skin surface (cleansing) and improving skin barrier (moisturizing). Attributes of effective moisturizers include occlusion, to seal in the water; humectant, to draw water into the stratum corneum; emollient, to improve the softness and smoothness of the skin; and barrier repair, to decrease TEWL through replacement and/or regeneration of the lipid bilayer.[24]

Specialized Cleansers for Acne

Whereas moisturizers seek to introduce natural ingredients back into the skin (eg, water, ceramides), cleansers are used to remove both natural and chemical substances. This makes cleansers more difficult for manufacturers to formulate and patients to use. The optimal cleanser removes sebum and debris while preserving intercellular lipids and moisturizing skin. Types of cleansers are presented in Table 1. Of all categories of cleansers, lipid-free cleansers have the lowest irritancy potential and do not influence the pH of the skin.[8] This makes lipid-free cleansers particularly well suited as being adjunctive therapies for patients experiencing adverse effects associated with the use of prescription acne therapies. Investigations have shown greater lipid-barrier preservation when using lipid-free cleansers, in comparison to a leading sensitive skin cleanser, 1% sodium lauryl sulfate solution, and even when washing with water only. Available lipid-free cleansers suitable for use in acne-prone skin are depicted in Table 2, and a decision framework for clinicians to use when selecting between these products is presented in Figure 1.

TABLE 1.

Types of Cleansers					
Type	**Ingredient**	**Irritancy Potential**	**pH**	**Cleansing Ability**	**Examples**
Lipid-free cleanser	Water, glycerin, cetyl-alcohol, stearyl-alcohol	Extremely low	--	Low	Cerave®, Aquanil®, Cetaphil®, La Roche Posay® Toleriane™
Soap	Fatty acid salt	High	9-10	High	Ivory®
Combar	Fatty acid salt, synthetic detergent	Medium	7-9	medium	Dial®, Coast®
Syndet	Synthetic detergent	Low	5.5-7	Low	Dove®, Olay®

TABLE 2.

Specialized Lipid-free Cleansers for Acne-prone Skin and Their Therapeutic Ingredients		
Product	**Property**	**Ingredients**
Cerave® Hydrating Cleanser	Foaming	Cetearyl alcohol, sodium lauroyl lactylate
	Humectant	Glycerin, hyaluronic acid
	Barrier repair	Ceramide 1, 3, 6-II, cholesterol, phytosphingosine, MVE® Technology
	Surfactant	Polyoxyl 40 stearate, polysorbate 20, sodium lauroyl lactylate
Cerave® Foaming Cleanser	Surfactant	Cocamidopropyl hydrosultaine, sodium lauroyl sarcosinate, sodium methyl cocoyl taurate, sodium lauroyl lactylate
	Moisturizer	Caprylic/capric glycerides, Ceramide 1, 3 and 6-II, cholesterol
	Anti-inflammatory	Niacinamide
Neutrogena® Ultra Gentle Daily Cleanser	Humectant	Glycerin, caprylyl glycol
	Surfactant	Cocamidopropyl betaine, lauryl glucoside, sodium cocoyl sarcosinate, disodium lauroamphodiacetate
Cetaphil® PRO Oil Removing Foaming Face Wash	Surfactant, antibacterial, foaming	Zinc coceth sulfate
	Humectant	Glycerin
	Anti-inflammatory	Dipotassium glycyrrhizate, zinc gluconate

FIGURE 1. A decision framework for clinicians to use when selecting between adjunctive over-the-counter cleansers for acne-prone patients.

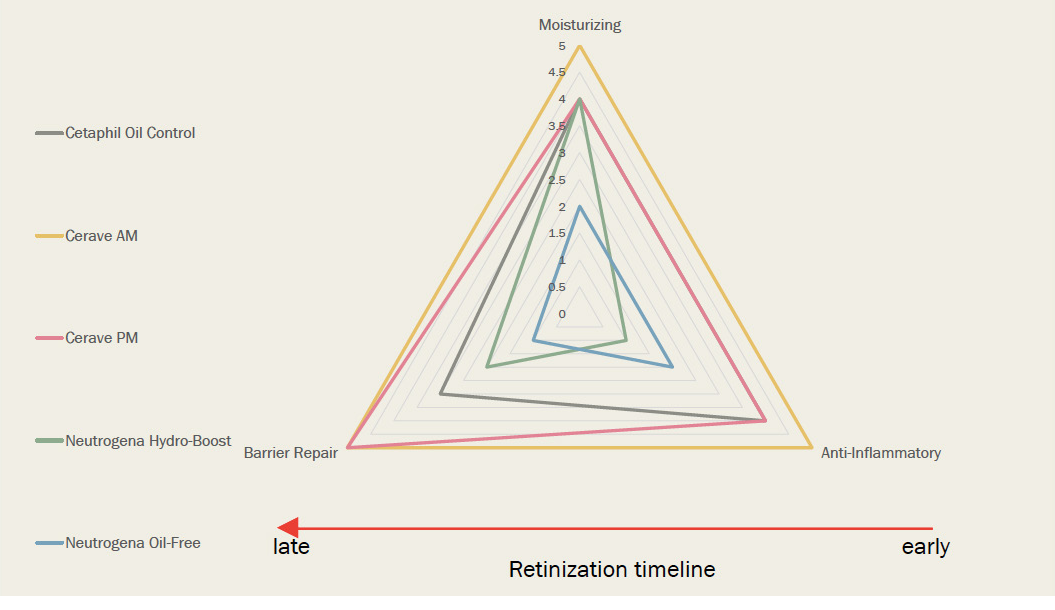


TABLE 3.

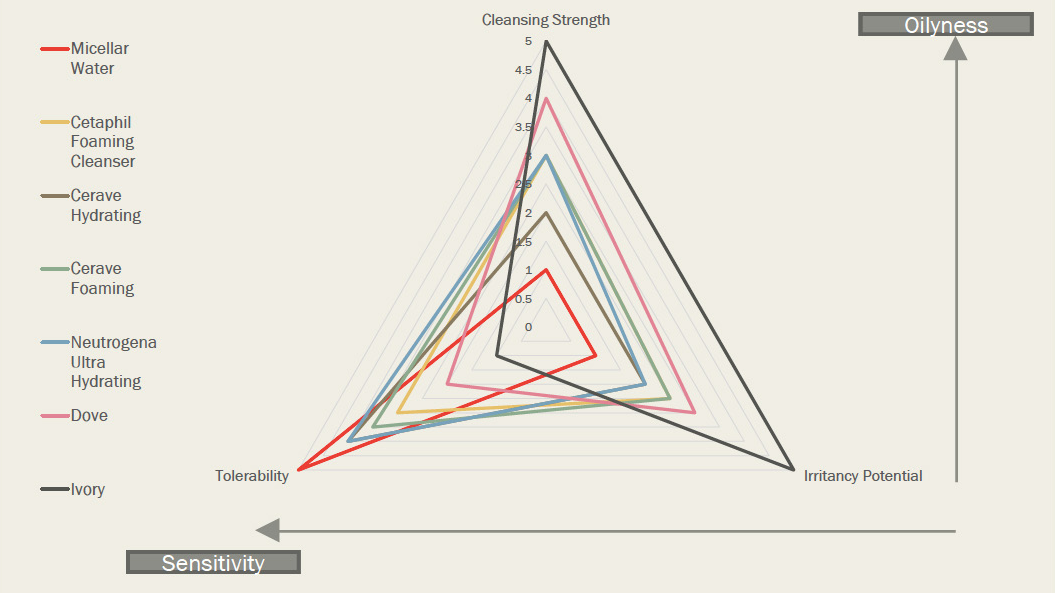
Specialized Moisturizers for Acne-prone Skin and Their Therapeutic Ingredients		
Product	**Property**	**Ingredients**
CeraVe® AM and PM Facial Moisturizing Lotions with SPF 30	Humectant	Glycerin, hyaluronic acid
	Emollient	Dimethicone
	Anti-inflammatory	Niacinamide
	Barrier replenishing	Ceramide 1, 3, 6-II, cholesterol, phytosphingosine in Multivesicular Emulsion (MVE®) Technology.
Neutrogena® Hydro Boost Water Gel	Humectant	Glycerin, sodium hyaluronate
	Emollient	Dimethicone, synthetic beeswax
Neutrogena® Oil-Free Moisture Broad Spectrum SPF 15	Humectant	Glycerin
	Anti-inflammatory	Glycerin soja
Cetaphil® PRO	Humectant	Glycerin
	Emollient	Dimethicone, isopropyl lauroyl sarcosinate, diisopropyl sebacate
	Oil absorber	Silica, polymethyl methacrylate, aluminum starch octenylsuccinate
	Anti-inflammatory	Tocopheryl acetate, glycyrrhetinic acid, zinc gluconate
	Barrier replenishing	Hydroxypalmitoyl sphinganine (Ceramide Technology™), pseudoceramide mimics, ceramide 5

Specialized Moisturizers for Acne

Moisturizers have the potential to offset the negative dermatological effects of prescription acne treatments (eg, erythema, irritation, inflammation, xerosis). They can also be important adjunctive therapies for acne patients if they are non-comedogenic, devoid of skin irritants, and compatible with treatment regimens.[53] A consensus statement from eleven Canadian dermatologists with expertise in treating acne stated that "ceramide-containing moisturizers may enhance adherence and complement existing acne therapies. The panel, therefore, proposes that adjunctive therapy with moisturizers and ceramide-containing moisturizers should be considered in acne-treated patients".[24] Although there are a plethora of skincare moisturizers available on the market, few studies have evaluated their efficacy and compatibility for patients with acne-prone skin.[54]

CeraVe® AM and PM Facial Moisturizing Lotions with SPF 30 (L'Oréal S.A., Clichy, France) contain ceramides, niacinamide, and hyaluronic acid. These creams have been shown to significantly improve the appearance of dry skin conditions and patient's subjective assessments of the quality of their professional life, self-image, and social life.[78] These creams are formulated using new technologies for delivering ceramides,

FIGURE 2. A decision framework for clinicians to use when selecting between adjunctive over-the-counter moisturizers for acne-prone patients.



including multivesicular emulsions, which deposit ceramides in a time-release manner for a continuous effect.[79] Cetaphil® PRO (Galderma Laboratories, L.P., Fort Worth, TX) is an oil-absorbing moisturizer that has been specially formulated for the enhanced treatment of acne-prone skin. Numerous trials have demonstrated its non-comedogenicity, non-acnegenic, and potential for photoprotection and reducing cutaneous irritation.[53,56] Through the incorporation of sebosuppressive and sebum-absorbent ingredients (Table 3) and Ceramide Technology™, Cetaphil® PRO reduces oil (sebum), simultaneously prevents TEWL while enhancing skin hydration and inducing increased endogenous production of ceramides.[53] Neutrogena® Hydro Boost Water Gel and Oil-Free Moisture Broad Spectrum SPF 15 creams alone and in combination have been investigated. A 12-week evaluator-blinded, randomized trial in males and females with mild-to-moderate acne vulgaris revealed that the concomitant use of these creams with an acne treatment resulted in improvements with overall inflammatory lesion redness, inflammatory lesion size, tactile surface roughness, uneven skin tone, skin blotchiness and a lack of skin clarity. These beneficial effects appeared across a wide range of subject ages, races, and Fitzpatrick skin types.[60] This study exemplified the suitability of these creams as adjuncts to acne treatments. A decision framework for clinicians to use when selecting between these products for acne-prone patients is presented in Figure 2.

Limitations

As only English-language publications were considered, a possible selection bias may have been present. In addition, many of the clinical trials included a short duration of follow up (eg, 28 days) and, as such, may have reduced the likelihood of documenting long-term improvements.

CONCLUSION

Acne is associated with a disruption to the skin's barrier function. This may present as a reduction in water-binding capacity and ceramide concentration, which can lead to dry skin and irritation. Systemic and topical treatments for acne can exacerbate these adverse effects. Informing clinicians about skin barrier dysfunction in acne and the benefits of adjunctive skincare may help them to choose the right product(s) to complement prescription therapy.

DISCLOSURES

The authors have no conflicts of interest to declare.

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AUTHOR CORRESPONDENCE

Anneke E. Andriessen PhD
E-mail:..... anneke.a@tiscali.nl

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

At-Home Transvaginal Device Following Fractional Carbon Dioxide Laser Treatment for Genitourinary Syndrome of Menopause

Macrene Alexiades MD PhD
Yale University School of Medicine, New Haven, CT
Dermatology and Laser Surgery Center of New York, New York, NY

ABSTRACT

Background: Device-based therapeutic approaches have been developed to treat women's genitourinary post-menopausal symptoms. Fractional carbon dioxide laser resurfacing ($FxCO_2$) has been demonstrated to be safe and effective in the treatment of GSM symptoms, however the results begin to wane by 12-months post-treatment.

Objective: This study aims at assessing the application of an at-home transvaginal red and infrared light device as a maintenance treatment commencing 12 months following $FxCO_2$ laser treatment for genitourinary syndrome of menopause (GSM).

Study Design: Subjects completing 12-month follow-up after three fractional CO_2 laser vulvovaginal treatments received an at-home device and monitored for GSM symptoms with long-term follow-up to 12 months (2 years post-laser).

Methods: 10 post-menopausal subjects completing 12-months follow-up after three $FxCO_2$ vulvovaginal treatments for GSM were treated with an at-home red and infrared LED device. Treatment consisted of intravaginal application three times per week, and subjects were followed to 1, 3, 6, and 12 months. Subjects completed the vaginal assessment scale subject satisfaction, and QUID to assess for vulvovaginal and stress urinary incontinence (SUI) symptoms.

Results: Vulvovaginal symptoms measured by VAS were mean 89% improved at 12-month follow-up after $FxCO_2$ and maintained at 73% improved over baseline (2 years post-laser) following an additional 12 months of at-home transvaginal light therapy ($P<0.05$). VAS symptoms gradually increased over the 12 months maintenance period by a mean of 17% ($P<0.05$). Mean subject satisfaction was 0 at baseline, 1.86 at 1 year following $FxCO_2$, and 1.00 after an additional 1 year of at-home light therapy. SUI symptoms as measured by QUID were mean 81% improved at 12-month follow-up after FxCO2and maintained at 38% improved over baseline (2 years post-laser) following an additional 12-months of at-home light therapy ($P<0.05$). SUI symptoms gradually increased by a mean of 43% over the 12-month maintenance period ($P<0.05$).

Conclusions: At-home transvaginal red and near infrared light therapy commencing at 12 months post-$FxCO_2$ vulvovaginal treatment in a post-menopausal population maintained statistically significant improvements in vulvovaginal and SUI symptoms over the additional 12-month period (2 years post-laser); however, a gradual return of symptoms suggests that laser re-treatment or combination with hormone therapy may be necessary to maintain optimal outcomes.

J Drugs Dermatol. 2020;19(11):1076-1079. doi:10.36849/JDD.2020.1012

INTRODUCTION

Device-based therapeutic approaches are being focused on women's genitourinary health to provide hormone-free non-surgical treatment alternatives for menopausal vaginal and urinary signs and symptoms defined as genitourinary syndrome of menopause (GSM).[1-3] Several lasers, including fractional carbon dioxide ($FxCO_2$), erbium:yttrium aluminum garnet (Er:YAG), and hybrid 1470-nm diode, and radiofrequency (RF) devices, are FDA cleared for vaporization, incision, excision, ablation, or photocoagulation of genitourinary tissue. Fractional CO2 (10,600 nm), Er:YAG (2940 nm), and diode (1470 nm) lasers create microcolumns of vaporized or thermally denatured tissue in the vulva and vagina, stimulating histological findings of thickened glycogen-rich epithelium, fibroplasia, neocollagenesis, angiogenesis, and restoration of papillation, which correlate with clinical improvements in GSM signs and symptoms.[1-6] An at-home red and infrared light device has been demonstrated in published studies to improve vaginal health on validated scales and indices and may provide practical alternative to in office procedures.[7,8] $FxCO_2$ has been shown to improve the signs and symptoms of vulvovaginal atrophy (VVA) and stress urinary incontinence (SUI), however the results begin to wane between 6 and 12 months post-treatment.[9,10] A post-menopausal population that completed 12-month follow after a series of $FxCO_2$ vulvovaginal treatments were subsequently treated with an at-home red and infrared LED vaginal device with long-term follow-up to 1 year.

PATIENTS AND METHODS

Patients

10 post-menopausal subjects completing 12-month follow up following three $FxCO_2$ treatments to the vulva and vagina for GSM were enrolled for treatment with an at-home red and infrared

LED device. Study participants included postmenopausal women with symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia) and SUI (urine leakage when coughing, sneezing, bending, jogging, exercising, and urgency). Study inclusion criteria included: absence of menstruation for at least 12 months; unresponsive to or dissatisfied with previous local estrogen therapy (with a washout period for the use of hormone replacement therapy, either systemic or local, within the six months prior to study enrollment); desire to maintain sexual activity and currently experiencing sexual activity at least once a month. Exclusion criteria included: previous vaginal reconstructive surgery or treatment for vaginal tightening within the past 12 months; previous laser or RF treatment within the prior six months; prolapse stage ≥ II, according to the pelvic organ prolapse quantification (ICS-POP-Q) system; acute or recurrent urinary tract infections; active genital infections; undiagnosed vaginal bleeding; anticoagulation medications one week prior to and during the treatment course; currently using immunosuppressive medications or use of systemic corticosteroid therapy six months prior to and throughout the course of the study; suffering from hormonal imbalance or any serious disease or chronic condition that could interfere with study compliance excluded participation in the study.

Treatment

The at-home transvaginal device (vFit+, Joylux Inc., Washington, DC) is FDA cleared as a general wellness product, intended to increase sexual pleasure, and for personal wellness to improve confidence with sexual intercourse (C170094). It incorporates low-level light therapy via light emitting diodes (LED) in the red and near-infrared wavelength spectrum (662–855 nm), heat (~41°C), and therapeutic vibration (80–110 Hz). The device heats the vaginal surface to 41C (38.6–44.1C). The device also employs vibration at 80–110 Hz for up to 10-minute treatment sessions. In the current study, the silicone-encased device was inserted into the vagina for 10 minutes per treatment session three times per week. A water-based lubricant consisting of water, glycol, and hydroxyethyl cellulose aids device insertion and assists in transmission of light energy into the vaginal tissues. Treatment consisted of intravaginal application three times per week.

Assessments

Subjects were followed up at 1, 3, 6, and 12 months. Subjects completed the vaginal assessment scale (VAS), subject satisfaction, and Questionnaire for Urinary Incontinence Diagnosis (QUID) to assess for vulvovaginal and urinary symptoms.

Statistical Analysis

The two-tailed t-test was performed to determine whether differences between treatment timepoints, prior to treatment, and to baseline, were statistically significant.

RESULTS

Demographics

All subjects were post-menopausal females. The mean subject age was 54 (range, 44–64). 80% were skin phototype 1–3 and 20% were skin phototype 4–5.

Vulvovaginal Symptoms

Vulvovaginal symptoms compared to baseline as measured by VAS were mean 89% improved at 12-month follow-up following $FxCO_2$ laser resurfacing and maintained at 73% improved following an additional 12 months of treatment with the at-home transvaginal device (P<0.05, Figure 1). VAS symptoms gradually increased during the 12-month at-home light maintenance treatment period, with a mean 17% return towards baseline (P<0.05).

Subject Satisfaction

Mean subject satisfaction was 0 at baseline, 1.86 at 12 months following $FxCO_2$ treatment, and 1.00 following 12 months of at-home light therapy.

Stress Urinary Incontinence

Stress urinary incontinence (SUI) symptoms as measured by QUID were mean 81% improved at 12-month follow-up following fractional CO_2 laser resurfacing and treatment with at-home light device resulted in a maintenance of 38% improved at 12-months of treatment compared to baseline (P<0.05). SUI symptoms gradually increased during the 12-month at-home light maintenance treatment period, with a mean 43% return towards baseline over 12 months (P<0.05).

FIGURE 1. Maintenance of post-laser vulvovaginal symptoms with at-home light therapy. VAS symptoms during 12-month period of treatment with an at-home transvaginal device commencing 12 months after fractional CO_2 laser treatment in a post-menopausal population.

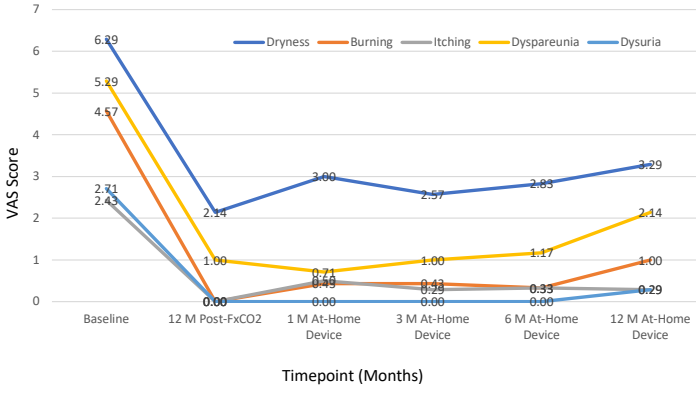


FIGURE 2. Subject Satisfaction Prior to Treatment, 1 Year Following $FxCO_2$ Laser, and Over 1 Year of At-Home Transvaginal Light Treatment. Satisfaction scale -2 = very dissatisfied, -1 = dissatisfied, 0 = uncertain, 1= satisfied, 2= very satisfied.

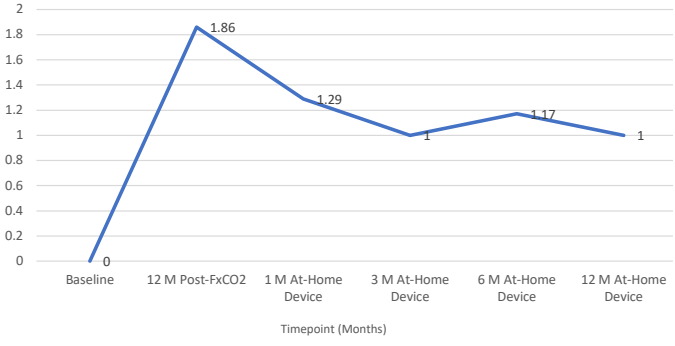
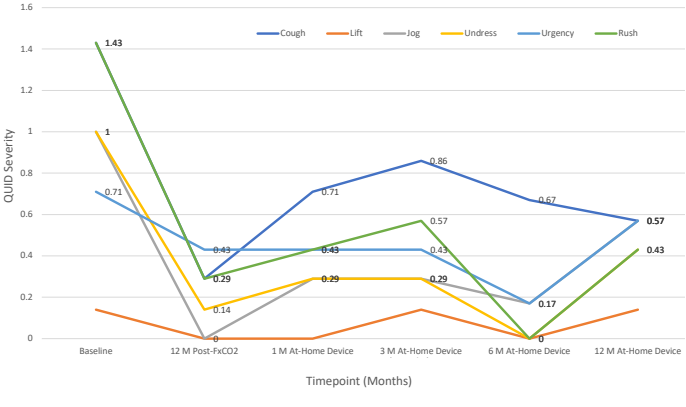


FIGURE 3. Stress urinary incontinence symptoms during 12-month period of at-home vaginal light therapy commencing at 12 months following fractional CO_2 laser treatment. Subjects received at-home transvaginal light device at 12 months following $FxCO_2$ laser and were monitored for SUI symptoms as measured by QUID over an additional 12-month period.



DISCUSSION

When utilized commencing at 12 months post-$FxCO_2$ vaginal laser treatment, the at-home transvaginal device maintained a 73% improvement in vulvovaginal symptoms over the course of an additional 12 months (2 years post-$FxCO_2$ laser treatment; $P<0.05$; Figure 1). A gradual recurrence of symptoms was observed but at a much slower rate than prior to treatment. Vulvovaginal symptoms began to increase following $FxCO_2$ with a 12% worsening in mean VHI scores between 6 and 12-month follow-up.[9,10] In the current study, maintenance treatment from 12-to-24 months follow-up after initial $FxCO_2$ resulted in a 17% worsening over the course of one year, suggesting a slowing in the rate of vulvovaginal symptom recurrence. It is possible and deserving of further study that commencement of at-home light treatment by 6 months post-$FxCO_2$ laser treatment completion would result in improved maintenance of clinical outcomes.

SUI symptoms as measured by QUID were 38% improved at 12 months of treatment with the at-home transvaginal device compared to baseline (2 years post-$FxCO_2$ laser treatment; $P<0.05$). This decline represents a more significant worsening in SUI symptoms, which were a mean 81% improved at 12-month follow-up following $FxCO_2$. SUI symptoms gradually increased during the 12-month at-home light maintenance treatment period, with a mean 43% return towards baseline over 12 months (2 years post- $FxCO_2$ laser treatment; $P<0.05$). Prior studies demonstrated improvement in SUI following treatment with this at-home transvaginal device in 84% of patients with >50% improvement and a reduction in the 1-hour median pad weight test from 18 g to 0 g.[7] The urogenital Distress Inventory Short Form (UDI) improved in 92% >50% and Incontinence Impact Questionnaire Short Form (IIQ improved in 85% and decreased by 69%).[8]The decline in the maintenance of improvement on the QUID reported here may be attributed to the study design; the scores at the commencement of at-home treatment likely require greater therapeutic efficacy in order maintain the improvements from $FxCO_2$ laser therapy. As compared to vulvovaginal signs and symptoms, SUI may require more frequent retreatment with laser, earlier maintenance treatment, and/or combination of at-home light treatment with topical therapy in order to maintain outcomes.

The remodeling and rejuvenation of the vulvovaginal tissue with transvaginal red and infrared light correlates with clinical outcomes with a similar mechanism of action to laser vaginal treatment. After 10 minutes of use, the mean temperature at the surface of the device measured via thermocouple has been reported at 41.2°C (range, 38.6° to 44.1°C).[7] On histology, the at-home light therapy device has been shown to induce collagen and elastin production in fibroblasts. This production was proportional to the duration of exposure.[8] These findings suggest a similar mechanism of action, albeit at lower efficacy rates, to $FxCO_2$ rejuvenation of vaginal tissue, which induces the restoration of the vaginal thick squamous stratified epithelium, increased epithelial glycogen, glycogen-rich shedding cells at the epithelial surface, and neocollagenesis, angiogenesis, and new ground substance in the lamina propria.[11] In the case of both the at-home transvaginal light device described herein and in $FxCO_2$ laser treatment of the vagina, these findings correlate with clinical relief from GSM symptoms.

Diminishing estrogens during menopause result in a decrease in vaginal epithelial glycogen, causing depletion of *Lactobacilli*, consequent rise in pH, overgrowth of yeast forms, and pathogenic bacteria leading to many of the signs and symptoms of GSM.[12] The chronic inflammation and colonization with pathogenic species results in atrophy, vaginitis, and recurrent urinary tract infections. Through its induction of thickened, glycogen-rich vaginal epithelium, $FxCO_2$ laser treatment has been demonstrated to restore the *Lactobacillus* population and

normal acidic pH, thereby reversing the chronic irritation and recurrent urinary tract infections associated with menopause.[12] Further research is needed to determine whether a similar microbiome mechanism applies to other vaginal devices, such as the at-home red and infrared light device described here.

CONCLUSION

At-home transvaginal red and near infrared LED light therapy commencing 12 months following fractional CO_2 laser treatment maintains statistically significant improvements in GSM symptoms for an additional 12 months (2 years post-laser treatment). The gradual return of vulvovaginal symptoms towards baseline that occurs post-laser treatment was slowed by the adjuvant use of the at-home technology. More research is required to reproduce these findings and determine the rate of reduction in the frequency of re-treatment with laser or the need for topical hormone therapy.

DISCLOSURES

Dr. Alexiades has served on the medical advisory board of JoyLux, Inc. No funding was received for this study. This is a self-funded study by the investigator.

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AUTHOR CORRESPONDENCE

Macrene Alexiades MD PhD
E-mail:..... dralexiades@nyderm.org

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ORIGINAL ARTICLE

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Variables Affecting Delivery of Glycopyrronium Tosylate Through Human Skin In Vitro

Franceso Caserta,[a] Jon Lenn PhD,[a] Hans Hofland PhD[b]

[a]MedPharm, Durham, NC

[b]Dermira, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Menlo Park, CA

ABSTRACT

Background: Hyperhidrosis is a condition characterized by excessive sweating beyond what is required for normal thermal regulation. It can involve multiple body areas including the axillae, palms, soles, or craniofacial regions. Glycopyrronium tosylate (GT) is a topical anticholinergic approved by the FDA (2018) for treatment of primary axillary hyperhidrosis in patients 9 years and older.

Objective: Gain insight into variables (anatomical sites, occlusion, exposure time) affecting GT delivery into human skin.

Methods: Human skin from different anatomical regions (palmar, plantar, axillary, and abdominal skin) was mounted into flow-through diffusion cells (MedFlux-HT®). GT solution (2.4%) was applied at 10 mg/cm^2 and the receiving fluid was collected every 2 hours, for 24 hours. GT penetration was determined using LC/MS/MS. The effect of occlusion was assessed by covering the skin with either parafilm or saran wrap, and the effect of exposure time was assessed by incubating the skin for 5, 15, or 60 minutes before washing off the GT from the surface.

Results: GT delivery through palmar and plantar skin was up to 40-fold lower compared to delivery through axillary or abdominal skin. Occlusion increased GT delivery up to 10-fold. Reducing exposure time from 24 hours to either 5, 15, or 60 minutes, decreased GT flux by 90%. However, occlusion during these varied exposure times was able to restore GT delivery to levels found in the 24-hour exposed, non-occluded control group.

Conclusion: These in vitro skin penetration studies showed that skin thickness, exposure time, and occlusion substantially influenced GT delivery, potentially impacting clinical trial design.

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INTRODUCTION

Hyperhidrosis is a condition of excessive sweating beyond what is physiologically required to maintain normal thermal regulation. Hyperhidrosis affects an estimated 4.8% of the US population, which amounts to approximately 15.3 million people.[1,2] The adverse impact of hyperhidrosis on quality of life has been well documented,[2,3] and a recent case-control study found that anxiety and depression are >3.5 times more prevalent among patients with hyperhidrosis than those without.[4] Hyperhidrosis treatments may work to block sweat from reaching the skin surface (eg, topical antiperspirants), inhibit neuronal transduction to sweat glands (eg, injectable onabotulinumtoxinA or off-label use of oral anticholinergic drugs), destroy the sweat glands (eg, thermal ablation or surgical removal), or via unknown mechanisms (eg, iontophoresis).[2,5,6] These treatments vary greatly with respect to effectiveness, invasiveness, and side effects, and only three of these treatments are approved by the U.S. Food and Drug Administration (FDA) for axillary hyperhidrosis, including topical aluminum salts, onabotulinumtoxinA injections, and a microwave device for thermal ablation of sweat glands. Recently, glycopyrronium tosylate (GT), an acetylcholine receptor antagonist, was approved by the U.S. FDA in 2018 as a novel, once daily topical treatment for primary axillary hyperhidrosis in patients 9 years of age and older (QBREXZA® [glycopyrronium] cloth, 2.4%, for topical use). Primary hyperhidrosis (excessive sweating without a known cause) is localized (focal), characteristically symmetric, and can affect the axillae, palms of the hands, soles of the feet, face, and other areas. Skin in other anatomical areas may be different from the axilla and therefore more studies are needed.

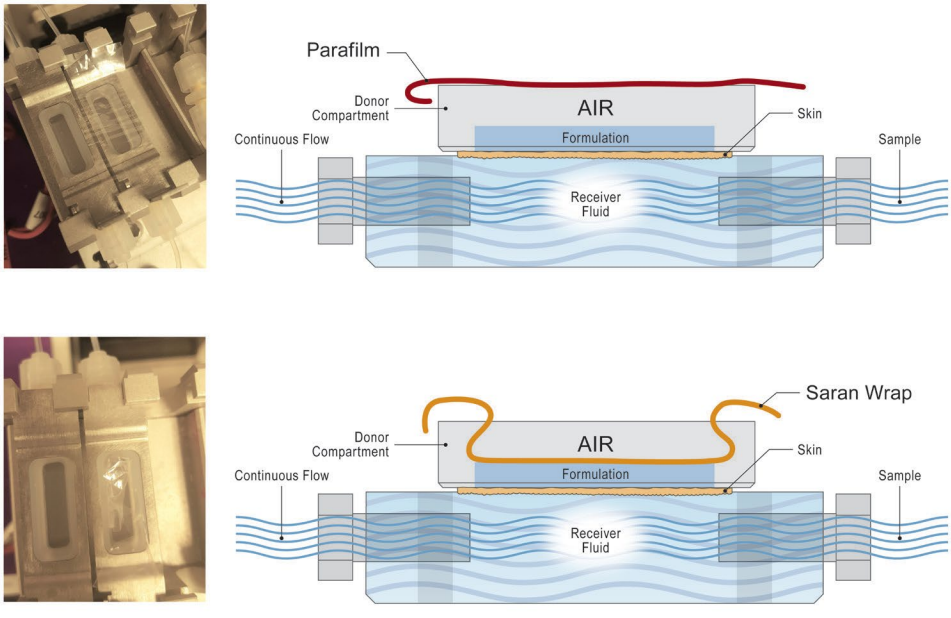
In the present studies, delivery of GT through skin from various anatomical sites, including the axillae, abdomen, palms, and soles, was investigated. The effect of occlusion was investigated as a means to increase delivery. Finally, the effect of exposure time (with and without occlusion) was investigated. GT was removed from the skin 5, 15, and 60 minutes after application.

MATERIALS AND METHODS

Analytical Method

A liquid chromatography with tandem mass spectrometry (LC/MS/MS) detection method was developed for the quantification of GT from the samples generated in this study. Briefly, the concentrations of GT were measured using an ultra-performance liquid chromatographic system (Nexera X2 Series UHPLC, Shimadzu) equipped with a triple quadrupole tandem

FIGURE 1. Schematic of MedFlux-HT® flow-through diffusion cell with parafilm (top) or saran wrap (bottom) used to mimic occlusion.



mass spectrometer (LCMS-8040, Shimadzu). Separation of GT was accomplished using a SupelcoTitan C18 column (2 cm x 2.1 mm, 1.9 µm) operated at 30°C. The mobile phase consisted of 5 mM ammonium formate with 0.01% formic acid and acetonitrile. The analysis was performed under gradient conditions with a flow rate of 0.400 mL/min. The MS spectra were acquired in the positive ion mode on the mass range 318.40–116.10 m/z for GT and 321.40–119.10 m/z for its internal standard deuterated-GT (GT-d3).

Skin Thickness (Anatomical Sites)

Skin from different anatomical regions (palmar, plantar, axillary, and abdominal skin) was obtained from 3 donors and tested (4 replicates for each skin region per donor). Full thickness skin samples were mounted into flow-through diffusion cells (MedFlux-HT®). GT solution (2.4%) was pressed from QBREXZA® cloths, applied at 10 mg/cm^2 and allowed to dry. The receiving fluid (phosphate buffered saline; PBS) was collected every 1–2 hours, for 24 hours, and GT penetration was quantified using LC/MS/MS.

After 24 hours, skin was taken from the diffusion cells and tested for penetration of GT into the epidermis and dermis. The epidermis and dermis were not able to be separated for the palmar and plantar skin, therefore, the penetration of GT was measured in the epidermis and dermis combined, for all anatomical sites. A solution of 90:10 v/v ethanol:water was used to extract GT from the skin samples, by homogenization followed by shaking for approximately 0.5 hour. GT levels were quantified using LC/MS/MS.

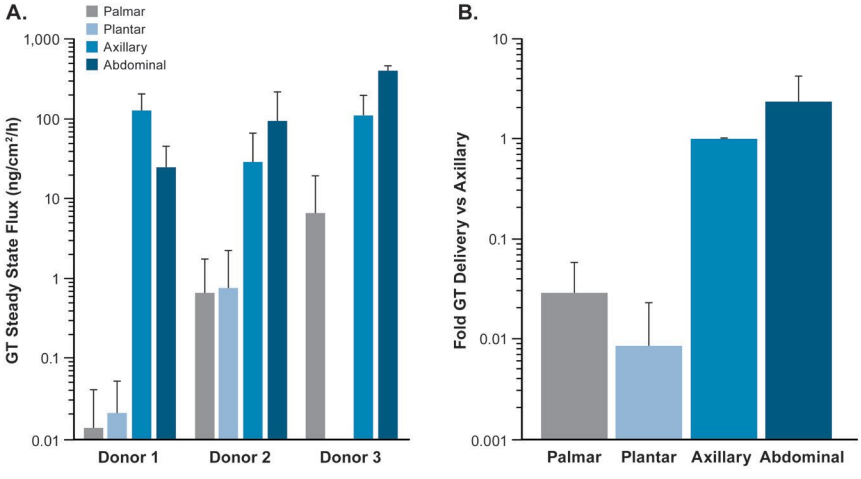
Occlusion

Human skin was obtained from elective abdominoplasty with donor consent under IRB approval (Study number 15-MEDP-101). The skin was dermatomed to a thickness of approximately 0.5 mm and mounted into flow-through diffusion cells (MedFlux-HT®). GT solution (2.4%) was applied at 10 mg/cm^2 and allowed to dry. After dosing, cells were either left un-occluded, or were occluded with parafilm or saran wrap. The plastic wrap was placed in direct contact with the skin while the parafilm was placed between the donor chamber and metal clamp creating a small space between the skin and parafilm. A schematic showing the occlusion with parafilm or saran wrap on the diffusion cells is illustrated in Figure 1. The receiving fluid (phosphate buffered saline; PBS) was collected every 1–2 hours for 24 hours, and GT penetration was quantified using LC/MS/MS.

Exposure Time

In order to enable distinct exposure times, a washing method to remove GT from the surface of the skin needed to be established. Six different washing solutions were tested as follows: human abdominal skin was placed on a piece of aluminum foil, and 1 cm^2 portions of skin were dosed with 10 mg of 2.4% GT solution. The GT solution was allowed to dry for approximately 5 minutes, followed by removal of the GT by wiping the skin surface with: 1) a dry cotton swab; 2) a cotton swab immersed in one of the six different wash-off solutions; 3) a wet cotton swab immersed in warm tap water to simulate a final rinse. The wash-off solutions consisted of one of the following: 1) warm water (38–40°C); 2) Dial® Gold hand soap (0.5% soap in water); 3) Dove® White bar soap (5% soap in water); 4) Dawn® Original dish soap (5% soap

FIGURE 2. (A) Steady state flux of GT (ng/cm²/hr) in palmar, plantar, axillary, and abdominal skin in three separate skin donors. GT absorption for plantar skin from Donor 3 was below the level of quantification (BLQ). (B) Fold change in steady state flux found in palmar, plantar, and abdominal skin compared to axillary steady state flux using data from combined donors. Bars represent the fold change of steady state flux compared to axillary steady state flux for each skin type for 3 donors. Error bars represent one standard deviation of the mean.



in water); 5) hand sanitizer (70% ethanol in water); 6) rubbing alcohol (70% IPA in water). To assess the amount of GT left on the surface of the skin after this washing procedure, the surface of the skin was wiped with 1) dry cotton swab; 2) cotton swab immersed in ethanol:water (9:1); 3) dry cotton swab; 4) one tape strip (D-squame tape). The three cotton swabs and one tape strip were combined and assayed for GT by LC/MS/MS. The amount of GT in the *stratum corneum* was assessed by tape stripping an additional 5 times. The GT was extracted from the tapes and cotton buds by shaking the samples for approximately 0.5 hour with an appropriate volume of 90:10 v/v ethanol:water.

The effect of exposure time, with and without saran wrap occlusion, on delivery of GT was then investigated by allowing the product (10 mg/cm²) to remain on skin for 5, 15 or 60 minutes, prior to removal using warm water and Dial® Gold liquid hand soap (99.5:0.5 w/w) using the method described above. The results were compared to GT that was allowed to remain on the skin surface for 24 hours (not occluded).

RESULTS

Anatomical Sites

The mean steady state flux of GT was greater in axillary and abdominal skin compared to palmar and plantar skin (Figure 2A). In general, similar delivery of GT was observed through axillary vs abdominal skin and for palmar vs plantar skin. In combined donors, there was a 2.4-fold increase in steady state flux of abdominal skin compared to axillary skin (Figure 2B). However, steady state flux in palmar and plantar skin were only 0.01- to 0.03-fold that of axillary skin.

FIGURE 3. (A) Mean cumulative amount of GT recovered from combined skin (epidermis and dermis) 12 hours post-application of GT solution in individual donors. (B) Mean amount of GT recovered from skin (epidermis and dermis) 12 hours post-application of GT solution in combined donors. Bars represent the mean cumulative amount of GT from 4 replicates and 3 donors (n=12 per skin type). Error bars represent one standard deviation of the mean.

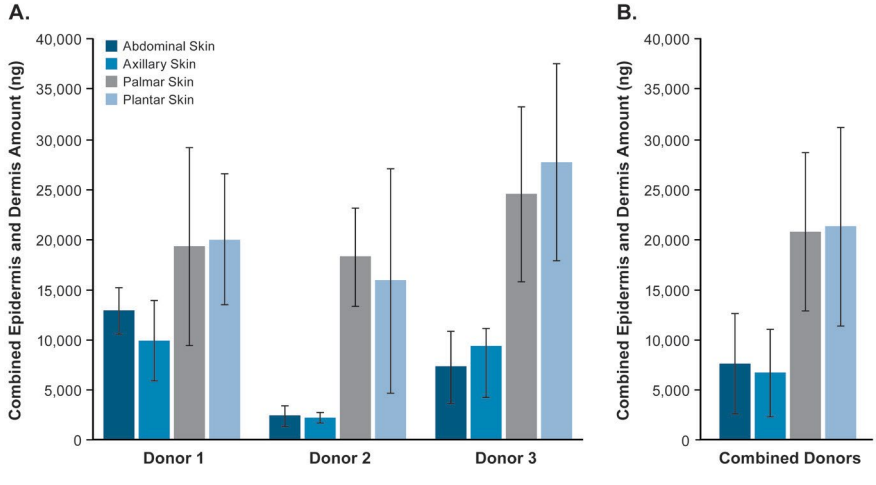
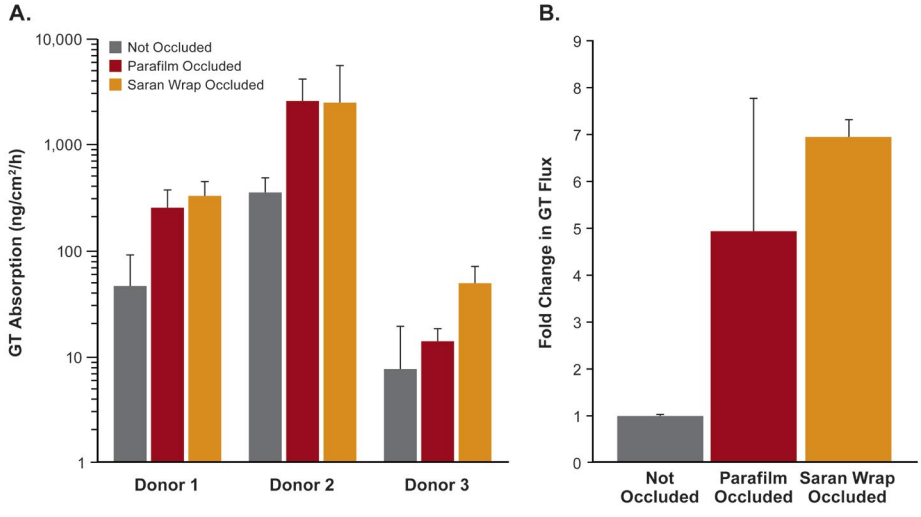


FIGURE 4. (A) Steady state flux of GT (ng/cm²/hr) in three separate skin donors in un-occluded, parafilm occluded, or saran wrap occluded skin. (B) Fold change in steady state flux compared to un-occluded samples following application of GT solution accompanied by parafilm or saran wrap occluded skin. Bars represent fold change in flux from three combined donors (n=2–4 replicates per donor). Error bars represent one standard deviation of the mean.



Less GT was recovered from abdominal and axillary skin than there was from palmar and plantar skin in individual donors (Figure 3A). In combined donors, the concentrations of GT (ng) recovered from palmar and plantar skin was approximately 2.5- to 3-fold greater than abdominal and axillary skin (Figure 3B).

Occlusion

After 24 hours of exposure, the mean steady state flux increased in each donor for occluded samples compared to un-occluded samples (Figure 4A). In combined donors there was a 5-fold increase in steady state flux in parafilm occluded samples, and a 7-fold increase in steady state flux in saran wrap occluded samples compared to un-occluded samples (Figure 4B). After shorter exposure times (see below), occlusion increased the delivery of GT by an average of 8.6-fold, and in some instances well over 10-fold (Figure 5).

Exposure Time

A study was performed to test the effectiveness of different washing methods for removing GT from the surface of the skin (Table 1). It was determined that 0.5:95.5 w/w hand soap:water should be used in this set of experiments.

FIGURE 5. (A) Steady state flux of GT (ng/cm²/hr) in four separate skin donors under various occlusion and wash-off conditions. (B) Percent of steady state flux of GT compared to un-occluded/no-wash off controls, in all skin donors combined under various occlusion and wash-off conditions. Bars represent percent difference in combined donor (4 donors, 3–4 replicates per donor). Error bars represent one standard deviation of the mean.

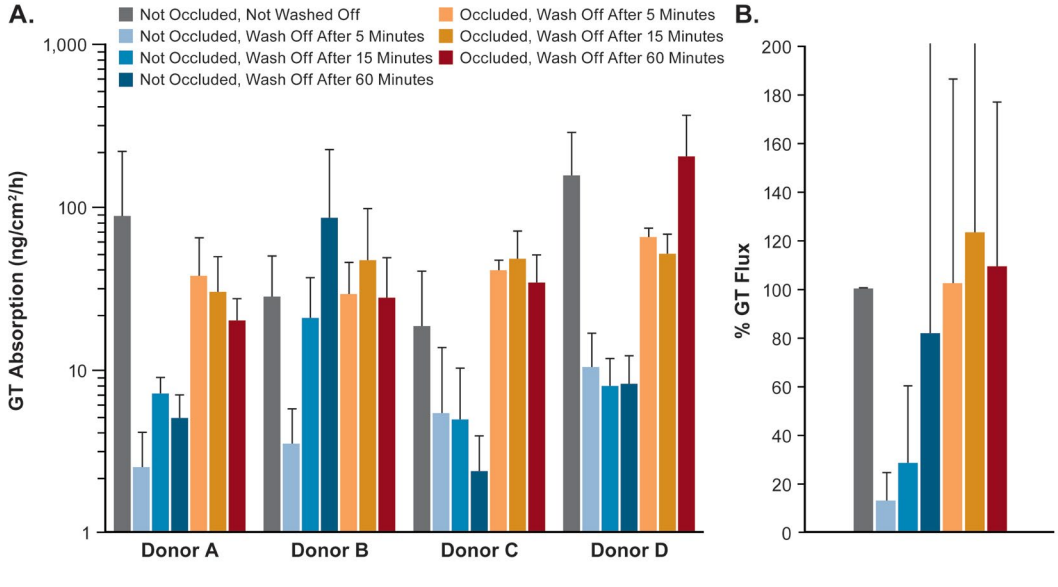


TABLE 1.

Recovery of GT Following Application and Wash-Off. Mean amount of GT (ng) and % amount of GT (calculated as % of applied dose) recovered from the stratum corneum and surface of the skin following application of 2.4% GT solution (~10 mg/cm^2) and subsequent wash-off. Data represent mean amount of GT recovered (n=5-6 per wash off method) +/- standard deviation of the mean.

	Stratum Corneum		Surface	
Wash Method	Quantity on SC Mean (ng)	% GT Remaining	Quantity on Surface Mean (ng)	% GT Remaining
Hand soap	694	0.18%	1793	0.46%
70% IPA	957	0.25%	2817	0.73%
Dish soap	1258	0.33%	3062	0.79%
Germ-X	762	0.20%	3310	0.85%
Bar soap	5230	1.35%	5056	1.31%
Warm water	1664	0.43%	14791	3.82%

GT, glycopyrronium tosylate; SC, stratum corneum

Human abdominal skin samples obtained from four skin donors (4 replicates per donor) were exposed to GT for 5, 15, or 60 minutes and were either left un-occluded or were occluded with saran wrap during this time. After these exposure times, GT was washed off with the washing procedure. GT skin permeation was measured over 24 hours. The steady state flux in un-occluded samples was found to be reduced by 87-92% compared to the un-occluded/not washed off controls in samples, independent of exposure times in 3 out of the 4 donors (Figure 5). This suggested that short (5- to 60-minute exposure times) without occlusion greatly reduce steady state flux. Interestingly, occlusion, even as short as 5 minutes, improved steady state flux to levels that were near un-occluded, not washed off controls.

DISCUSSION

Human skin presents a formidable barrier to the entry of most compounds. It is governed by passive diffusion and by the thickness of the stratum corneum from various anatomical sites, physiochemical characteristics of the penetrant and vehicle, applied dose, and dosing regimen, including exposure times and occlusion. The *ex vivo* human skin penetration model is a well-validated tool for the study of percutaneous absorption and the determination of the pharmacokinetics of topically applied drugs. The model uses excised human skin mounted in specially designed diffusion chambers (static or flow-through) that allow the skin to be maintained at a temperature and humidity that match real use conditions. The product/formulation is applied to the surface of the skin and the penetration of the drug is measured by monitoring its rate of appearance in the receptor solution flowing underneath the skin samples. It offers the potential of carefully controlling the variables involved in topical delivery, such as dosing volumes, humidity (occlusion), temperature, skin thickness, exposure times, etc. that exist in the clinical situation.

Primary hyperhidrosis can affect various body sites, including the axillae, palms of the hands, soles of the feet, face, and other areas. Skin permeation experiments were performed to assess how GT penetrates skin obtained from different anatomical sites. Palmar, plantar, axillary, and abdominal skin samples were obtained from 3 human donors and were donor matched to avoid donor to donor variations. In general, GT showed similar levels of penetration in abdominal and axillary skin. In 2 of the 3 donors the abdominal skin was more permeable, whereas axillary skin was more permeable in the third donor. Similarly, GT showed comparable levels of penetration in palmar and plantar skin. In 2 of the 3 donors there was no difference between GT penetration through palmar or plantar skin. However, in the 3rd donor, no penetration of GT was observed through plantar skin, suggesting palmar skin would be more permeable. A reduced penetration of GT was observed into the palmar and plantar skin where a thicker stratum corneum exists compared to abdominal and axillary skin. Similar correlations between stratum corneum thickness and topical delivery of clobetasol proprionate have been observed.[7]

Occluding the skin is a well-known means to enhance skin penetration.[8] Two techniques were used to mimic occlusion in the patient. First, parafilm was stretched over the donor compartment leaving a small gap between the skin and the parafilm. Second, saran wrap was pushed into the donor chamber and onto the skin surface to provide more direct occlusion and minimize evaporation. Both occlusion methods yielded a robust and equivalent increase in GT delivery through human abdominal skin suggesting that a loss of delivery due to increased thickness of the stratum corneum (eg, palmar skin) can be compensated for by occlusion (eg, by wearing a plastic glove).

In an experiment testing 6 different wash-off solutions it was shown that even the least effective method, ie, wiping the skin with a cotton swab with warm water only, was able to remove 96% of GT from the skin surface. The best method: 0.5% hand soap solution in water was able to remove 99.5% GT. All other

methods resulted in greater than 98% removal of GT, suggesting a wide range of effective wash-off methods. It should be noted that the wash-off method used in this ex vivo experiment was very minimal, by wiping with a cotton swab. In a real-life situation where the patient uses ample water to rinse the hands, the GT removal is expected to be even more effective.

The impact of exposure time on skin permeation of GT was assessed by applying the GT solution for 5, 15, or 60 minutes and washing the GT off the skin by using a 0.5% hand soap solution in water. The steady state flux in short exposure times (5–60 minutes) without occlusion reduced steady state flux compared to approximately 10% of the 24-hour exposure controls. Interestingly, occlusion, even as short as 5 minutes, improved steady state flux to levels that were near the un-occluded and not washed off controls.

These studies suggest that when GT is applied to palmar (or plantar) skin of patients, the penetration is slower than if GT is applied to axillary skin. In addition, if GT is left on the palmar skin for only a short period of time (5–60 minutes) the amount of GT that penetrates the skin is even further reduced. Occlusion, however, will increase the GT delivery significantly, and may be required to compensate for decreased delivery due to 1) thicker stratum corneum and 2) shorter exposure times. These study data may inform future clinical trial designs.

DISCLOSURES

FC and JL are employees of MedPharm. MedPharm conducted the studies on behalf of Dermira, Inc. HH is an employee of Dermira, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Menlo Park, CA.

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AUTHOR CORRESPONDENCE

Hans Hofland PhD
E-mail:..... hans.e.j.hofland@gmail.com

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ORIGINAL ARTICLE

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Effects of Tazarotene 0.045% Lotion on Quality of Life in Patients With Moderate-to-Severe Acne

Leon H. Kircik MD,[a–c] Edward Lain MD MBA,[d] Michael Gold MD,[e,f] Bruce Katz MD,[a,g] Hilary Baldwin MD,[h] Eric Guenin PharmD PhD MPH,[i] Anya Loncaric MS,[j] Radhakrishnan Pillai PhD[j]

[a]Icahn School of Medicine at Mount Sinai, New York, NY
[b]Indiana University School of Medicine, Indianapolis, IN
[c]Physicians Skin Care, PLLC, Louisville, KY
[d]Austin Institute for Clinical Research, Austin, TX
[e]Gold Skin Care Center, Nashville, TN
[f]Tennessee Clinical Research Center, Nashville, TN
[g]JUVA Skin & Laser Center, New York, NY
[h]The Acne Treatment and Research Center, Brooklyn, NY
[i]Ortho Dermatologics, Bridgewater, NJ*
[j]Bausch Health US, LLC, Petaluma, CA*

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ABSTRACT

Background: In two phase 3 trials (NCT03168334, NCT03168321), participants with moderate-to-severe acne had significant symptom improvements after 12 weeks of treatment with tazarotene 0.045% lotion. Given the negative psychosocial effects of acne on patients, data from these studies were analyzed to evaluate quality of life in various subgroups.

Methods: Mean changes from baseline to week 12 in Acne-Specific Quality of Life (Acne-QoL) domain and item scores were analyzed in the pooled intent-to-treat (ITT) population and in participants who were categorized as follows: Evaluator's Global Severity Score (EGSS) score=3 ("moderate") or score=4 ("severe") at baseline; Acne-QoL total score ≥60 (better quality of life) or <60 (worse quality of life), based on the median score at baseline. Exploratory analyses based on sex and race were also performed.

Results: In the pooled ITT population (N=1614), Acne-QoL improvements were greater with tazarotene 0.045% lotion versus vehicle lotion, with significant differences in the acne symptoms domain, 3 acne symptom items, 2 self-perception items, 1 role-emotional item, and 1 role-social item (all $P<0.05$). Acne-QoL improvements with tazarotene 0.045% lotion were comparable between the EGSS subgroups. However, participants who self-reported worse quality of life at baseline (Acne-QoL total score <60) had notably greater improvements than those with better quality of life. Female and Black participants had greater Acne-QoL improvements than male and White participants.

Conclusions: Participants treated with tazarotene 0.045% lotion had significant quality-of-life improvements. Clinician-rated symptom severity appeared to have a smaller effect on Acne-QoL outcomes than participants' own assessments of quality of life.

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INTRODUCTION

Topical retinoids are a mainstay for the treatment of *acne vulgaris* (acne), a prevalent skin condition that affects an estimated 40–50 million people in the United States.[1,2] However, tolerability issues associated with retinoids (eg, skin irritation or dryness) can make it difficult for patients to adhere to treatment.

Tazarotene 0.045% lotion, which is approved for the topical treatment of acne in patients 9 years and older,[3] was developed using a new polymeric emulsion technology that encapsulates tazarotene and hydrating/moisturizing ingredients within an oil-in-water emulsion, separated by a three-dimensional mesh matrix.[4] This easily spreadable and easy-to-use formulation allows for uniform and optimal delivery of tazarotene on the skin at lower concentrations relative to conventional formulations, as demonstrated in a phase 2 trial in which tazarotene 0.045% lotion showed comparable efficacy to tazarotene 0.1% cream but with fewer adverse events.[5]

In two phase 3 trials that included patients with moderate-

to-severe acne, once-daily treatment with tazarotene 0.045% lotion significantly reduced inflammatory and noninflammatory lesions relative to vehicle lotion.[6] Both studies included the 19-item Acne-Specific Quality of Life questionnaire (Acne-QoL),[7] which showed improvements in patient-reported quality of life with tazarotene 0.045% lotion after 12 weeks of treatment. Given the psychosocial impact of acne on quality of life,[8,9] post hoc analyses of the phase 3 data were conducted to evaluate which aspects of the Acne-QoL were of greatest concern to study participants and the effects of tazarotene 0.045% on those domains.

METHODS

Study Design

Detailed methods for the two phase 3 studies (NCT03168334 and NCT03168321) have been reported.[6] In brief, both were multicenter, double-blind, randomized, vehicle-controlled, parallel group phase 3 studies. Key eligibility criteria included: male or female, age 9 years or older; moderate or severe acne (Evaluator's Global Severity Score [EGSS] of 3 or 4); 20–50 facial inflammatory lesions (papules, pustules, and nodules); 25–100 noninflammatory lesions (open and closed comedones); and ≤2 facial nodules. Eligible patients were randomized 1:1 to receive tazarotene 0.045% lotion or vehicle, applied once-daily to the face for 12 weeks. CeraVe® hydrating cleanser and moisturizing lotion (L'Oreal, NY) were provided as an option for optimal cleansing and moisturization of the skin. The study protocol was approved by institutional review boards or ethics committees at all investigational sites. Studies were carried out in accordance with principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. All patients or their legal guardians provided written informed consent.

Quality of Life Assessment

Quality of life was assessed using the Acne-QoL, which includes 19 items in 4 different domains: self-perception (items 1, 2, 3, 6, and 10); role-emotional (items 4, 5, 7, 8, and 9), role-social (items 11, 12, 13, and 14), acne symptoms (items 15, 16, 17, 18, and 19). For each item, participants were asked to rate the degree to which acne has affected them with a score of 0 ("extremely") to 6 ("not at all"). Higher scores indicated better quality of life, and a positive score change indicated improvement.

Post Hoc Analyses

All analyses were based on the pooled intent-to-treat (ITT) population, defined as randomized participants who were provided with study drug. Mean changes from baseline to week 12 in Acne-QoL domain and item scores were analyzed in the pooled ITT population using an analysis of covariance (ANCOVA) with treatment group as a factor and baseline score as a covariate; $P<0.05$ indicated statistical significance between tazarotene 0.045% lotion and vehicle lotion. The ANCOVA model was also used to investigate Acne-QoL outcomes in participants categorized by EGSS score at baseline (score of 3 [moderate acne symptoms] or 4 [severe acne symptoms]) and by median Acne-QoL total score at baseline in the pooled ITT population (score ≥60 [better quality of life] or <60 [worse quality of life]).

Because differences in sex and race had been observed between the EGSS subgroups and between the Acne-QoL subgroups, exploratory analyses were conducted in demographic subgroups. Mean changes from baseline to week 12 in Acne-QoL domain scores were analyzed descriptively in tazarotene-treated participants categorized by sex (male or female) and by race (Black or White).

RESULTS

Participants

In the pooled ITT population (N=1614), mean Acne-QoL domain scores at baseline were similar between participants who received tazarotene 0.045% and those who received vehicle lotion (Table 1). Relative to the subgroup with moderate acne symptoms at baseline (EGSS score=3; n=1467), the subgroup with severe acne symptoms (EGSS score=4; n=147) had fewer female participants (52.4% vs 67.3%) and Black participants (8.2% vs 17.0%). This trend was reversed in Acne-QoL subgroups. Relative to the subgroup with better patient-reported quality of life at baseline (total score ≥60; n=819), the subgroup with worse quality of life (total score <60; n=791) had more female participants (80.5% vs 52.0%) and Black participants (19.1% vs 13.4%). Mean age was comparable between EGSS subgroups (20.5 vs 19.8 years [score=3 vs score=4]) and between Acne-QoL subgroups (22.5 vs 18.6 years [score <60 vs score ≥60]).

Quality of Life Improvements

In the pooled ITT population, mean improvements from baseline to week 12 in Acne-QoL scores (domains and items) were generally greater in participants treated with tazarotene 0.045% lotion than in those who received vehicle lotion (Figure 1). Significant differences between tazarotene 0.045% lotion and vehicle lotion ($P<0.05$) were found as follows: the acne symptoms domain; 3 items within the acne symptom domain (bumps on face, bumps full of pus, concerned with scarring); 2 items within the self-perception domain (feel embarrassed, dissatisfied with appearance); 1 item within the role-emotional domain (feel upset), and 1 item within the role-social domain (interacting with opposite sex or same sex if applicable).

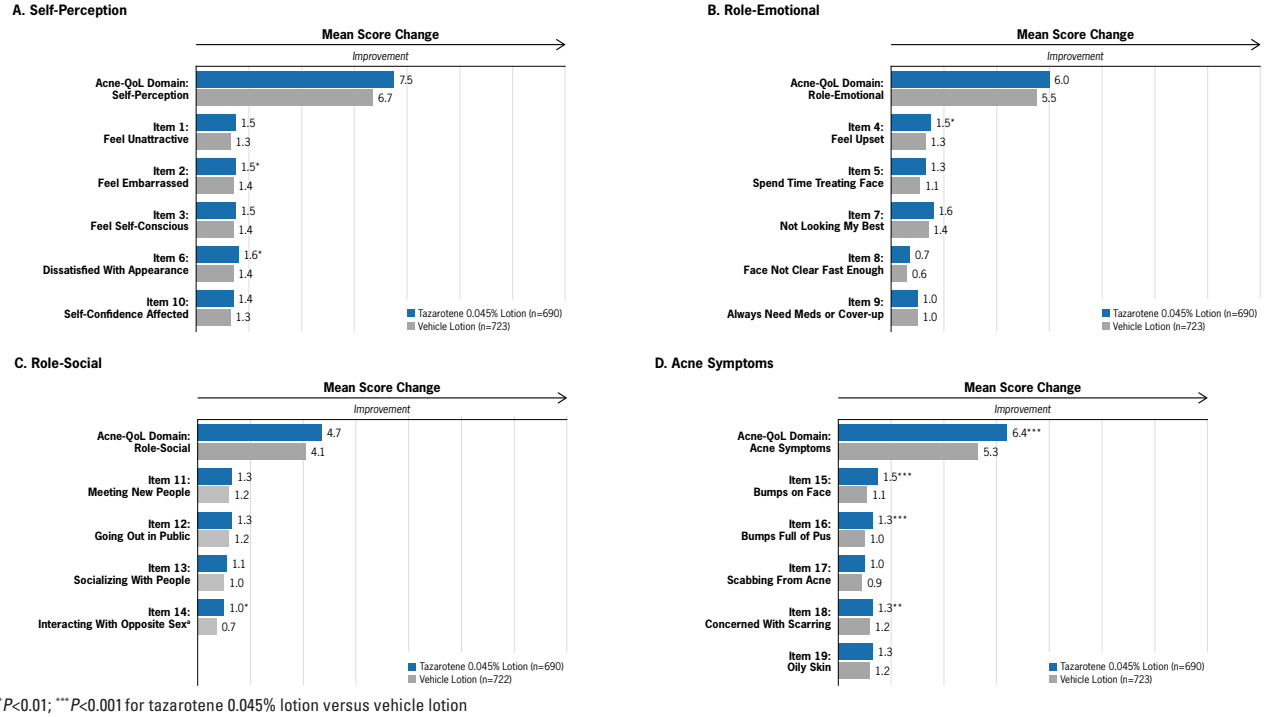
In the EGSS subgroups, the magnitude of Acne-QoL improvements with tazarotene 0.045% lotion was generally comparable between participants with moderate symptoms at baseline (score=3) and those with severe symptoms (score=4; Figure 2). In the EGSS score=3 subgroup, statistical significance for tazarotene 0.045% lotion was found in the acne symptoms domain and in 3 acne symptoms items (bumps on face, bumps full of pus, concerned with scarring; $P<0.05$ versus vehicle lotion;

TABLE 1.

Baseline Acne-QoL Scores and Severity Subgroups (ITT population, pooled)		
	Tazarotene 0.045% Lotion	Vehicle Lotion
Acne-QoL domains, ITT, mean score (SD)[a]	n=796	n=814[b]
Self-perception	19.9 (8.9)	20.2 (8.7)
Role-emotional	20.6 (8.3)	20.5 (8.3)
Role-social	19.2 (7.3)	19.3 (7.1)
Acne symptoms	19.3 (5.7)	19.4 (5.7)
EGSS subgroups, n (%)	n=799	n=815
Score=3 (moderate acne symptoms)	726 (90.9)	741 (90.9)
Female	490 (67.5)	497 (67.1)
Black	117 (16.1)	133 (17.9)
Score=4 (severe acne symptoms)	73 (9.1)	74 (9.1)
Female	41 (56.2)	36 (48.6)
Black	8 (11.0)	4 (5.4)
Acne-QoL subgroups, n (%)[c]	n=796	n=814
Total score ≥60 (better quality of life)	389 (48.9)	430 (52.9)
Female	198 (50.9)	228 (53.0)
Black	46 (11.8)	64 (14.9)
EGSS score=4	29 (7.5)	31 (7.2)
Total score <60 (worse quality of life)	407 (51.1)	384 (47.2)
Female	333 (81.8)	304 (79.2)
Black	78 (19.2)	73 (19.0)
EGSS score=4	44 (10.8)	43 (11.2)

[a]Score range is 0–30 for self-perception, role-emotional, and acne symptoms; range is 0–24 for role-social.
[b]n=813 for role-social.
[c]Based on the median Acne-QoL score in the pooled ITT population. Total score range is 0–114.
Acne-QoL, Acne-Specific Quality of Life questionnaire; EGSS, Evaluator's Global Severity Score; ITT, intent to treat; SD, standard deviation.

FIGURE 1. Mean changes from baseline in Acne-QoL scores (ITT population, pooled).



*P<0.05; **P<0.01; ***P<0.001 for tazarotene 0.045% lotion versus vehicle lotion
[a]Or same sex if applicable.
Acne-QoL, Acne-Specific Quality of Life questionnaire; ITT, intent to treat.

TABLE 2.

Effects of Tazarotene 0.045% Lotion on Acne-QoL Domain Scores in Demographic Subgroups (ITT population, pooled)

	At Baseline		At Week 12			
Acne-QoL Domain Subgroup	n	Mean Score (SD)	n	Mean Score (SD)	n	Mean Change (SD)
Self-perception						
Male	265	24.9 (8.2)	243	29.4 (5.9)	241	4.3 (6.7)
Female	531	17.4 (8.2)	449	26.9 (7.1)	449	9.2 (8.2)
White	589	20.4 (8.9)	511	28.0 (6.7)	509	7.2 (7.7)
Black	124	17.5 (8.8)	102	27.8 (7.3)	102	10.3 (9.7)
Role-emotional						
Male	265	25.2 (7.6)	243	28.2 (6.1)	241	2.9 (7.1)
Female	531	18.3 (7.6)	449	26.0 (7.6)	449	7.6 (8.5)
White	589	21.0 (8.3)	511	27.1 (6.9)	509	5.9 (7.9)
Black	124	18.2 (7.9)	102	26.8 (7.6)	102	8.5 (10.0)
Role-social						
Male	265	22.0 (6.7)	243	25.1 (4.6)	241	3.0 (5.7)
Female	531	17.8 (7.2)	449	23.7 (5.8)	449	5.6 (6.9)
White	589	19.7 (7.1)	511	24.5 (5.2)	509	4.4 (6.2)
Black	124	16.8 (7.5)	102	23.8 (5.9)	102	7.2 (8.0)
Acne symptoms						
Male	265	21.4 (5.5)	243	26.6 (4.7)	241	5.0 (5.8)
Female	531	18.3 (5.5)	449	25.7 (5.5)	449	7.1 (6.4)
White	589	19.7 (5.5)	511	26.2 (5.1)	509	6.2 (5.9)
Black	124	18.0 (6.4)	102	26.6 (5.3)	102	8.4 (7.8)

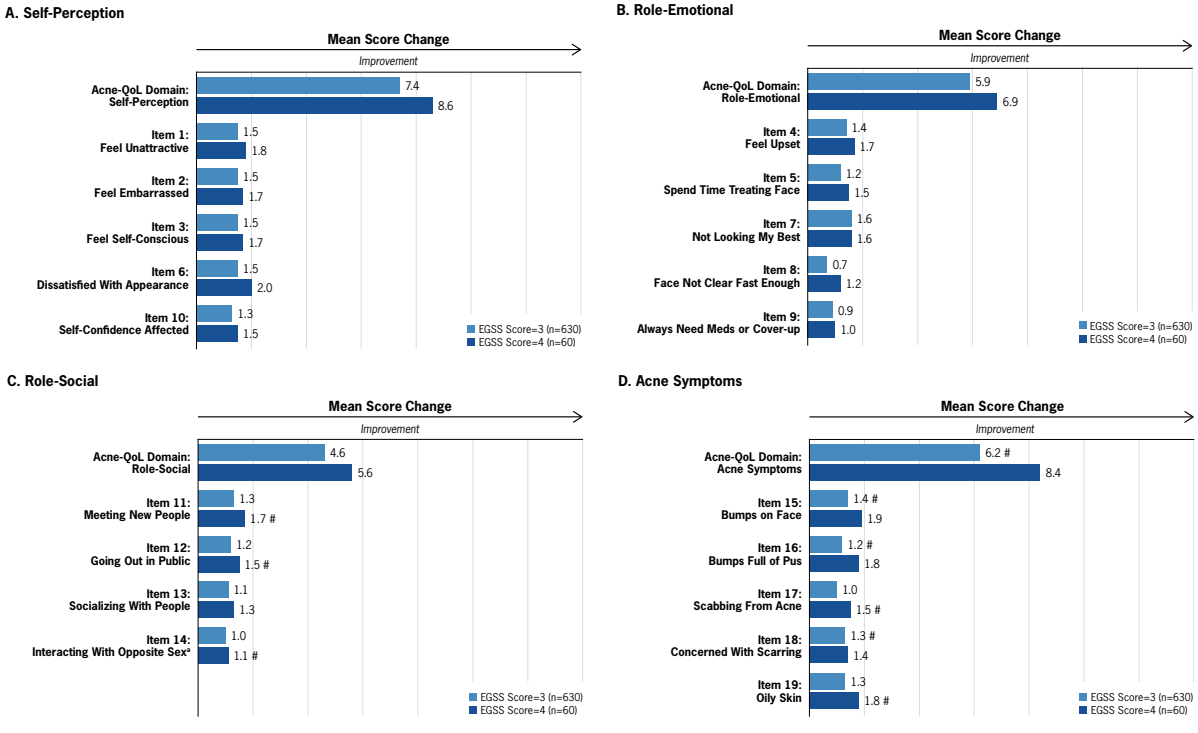
Acne-QoL, Acne-Specific Quality of Life questionnaire; ITT, intent to treat; SD, standard deviation.

data not shown for vehicle). In the EGSS score=4 subgroup, the difference between tazarotene 0.045% lotion and vehicle lotion was not statistically significant for the acne symptoms domain; however, significance was found in 2 acne symptom items (scabbing from acne and oily skin; $P<0.05$). Statistical significance in the EGSS score=4 subgroup was also found in 3 role-social items (meeting new people, going out in public, and interacting with the opposite sex or same sex if applicable; $P<0.05$).

Mean Acne-QoL improvements from baseline to week 12 were markedly greater in participants who self-reported worse quality of life at baseline (total score <60) than in participants with better quality of life (total score ≥60; Figure 3). In the Acne-QoL score ≥60 subgroup, statistical significance for tazarotene 0.045% lotion was found in the acne symptoms domain and in 2 acne symptoms items (bumps on face, bumps full of pus; $P<0.05$ vs vehicle lotion; data not shown for vehicle). In the Acne-QoL score <60 subgroup, statistical significance was also found in the acne symptoms domain, along with 3 acne symptom items (bumps on face, bumps full of pus, concerned with scarring; $P<0.05$). This subgroup with worse quality of life at baseline also had significantly greater mean improvements with tazarotene 0.045% lotion versus vehicle lotion in 1 role-emotional item (not looking my best) and 2 role-social items (meeting new people and interacting with the opposite sex or same sex if applicable; $P<0.05$).

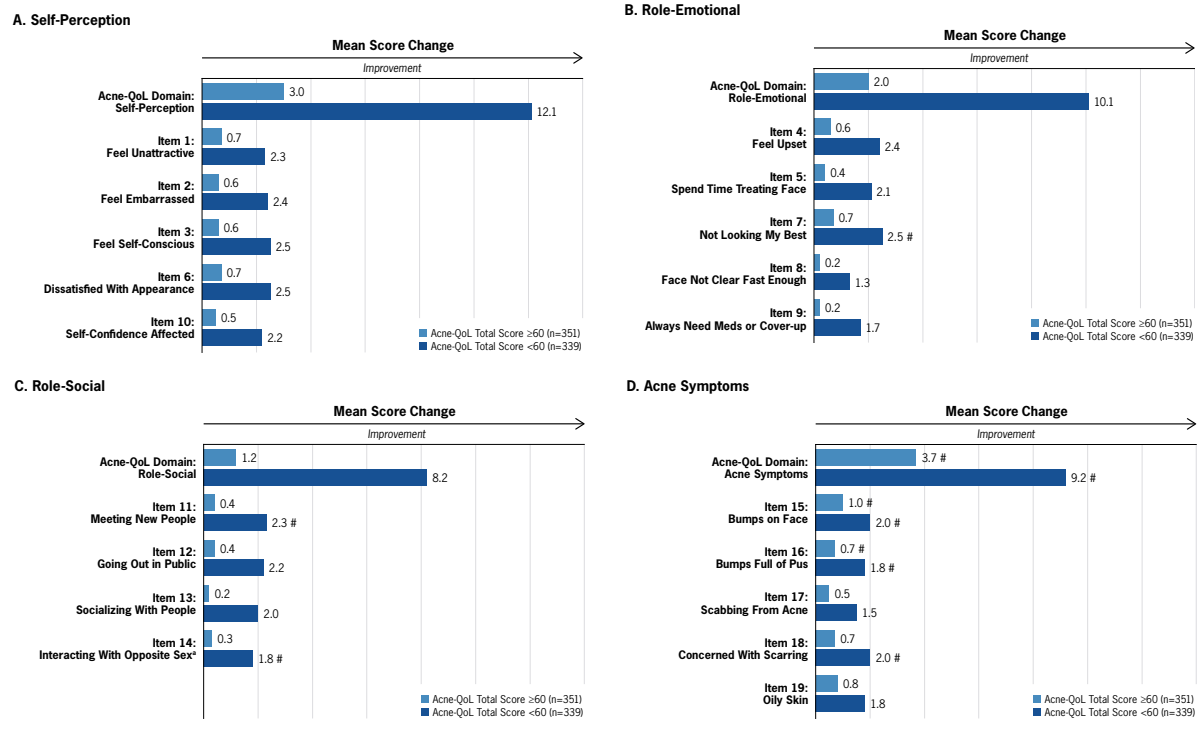
Exploratory analyses indicated that mean Acne-QoL domain scores at baseline were lower (worse) in female versus male participants, as well as in Black versus White participants (Table 2). However, mean improvements in female and Black participants were relatively greater than those in male and White participants, resulting in comparable Acne-QoL scores at week 12.

FIGURE 2. Mean changes from baseline in Acne-QoL scores with tazarotene 0.045% in EGSS subgroups (ITT population, pooled).



[#]*P*<0.05 for tazarotene 0.045% lotion versus vehicle lotion (data not shown for vehicle)
[a]Or same sex if applicable.
Acne-QoL, Acne-Specific Quality of Life questionnaire; EGSS, Evaluator's Global Severity Score; ITT, intent to treat.

FIGURE 3. Mean changes from baseline in Acne-QoL scores with tazarotene 0.045% lotion in Acne-QoL subgroups (ITT population, pooled).



[#]*P*<0.05 for tazarotene 0.045% lotion versus vehicle lotion (data not shown for vehicle).
[a]Or same sex if applicable.
Acne-QoL, Acne-Specific Quality of Life questionnaire; ITT, intent to treat.

DISCUSSION

Pooled data from two phase 3 studies indicate that participants with moderate-to-severe acne experienced improved quality-of-life with tazarotene 0.045% lotion, applied once daily for 12 weeks. In the pooled population, significant differences between tazarotene 0.045% lotion and vehicle lotion were found in the acne symptoms domain of the Acne-QoL, along with 3 items from that domain (bumps on face, bumps full of pus, and concerned with scarring). These results were consistent with the previously reported clinician-rated symptom assessments in the pooled population, which showed significantly greater reductions from baseline to week 12 with tazarotene 0.045% in inflammatory lesions (-57.9% vs -47.8% [tazarotene 0.045% vs vehicle]; $P<0.001$) and noninflammatory lesions (-56.0% vs -42.0%; $P<0.001$).[10]

To understand the potential effects of symptom severity on quality of life, Acne-QoL outcomes were analyzed in participants who had an EGSS score=3 ("moderate") or score=4 ("severe") at baseline. In participants treated with tazarotene 0.045% lotion, the magnitude of Acne-QoL score improvements was comparable between EGSS subgroups. However, statistical comparisons between tazarotene 0.045% lotion and vehicle lotion within each subgroup revealed some potential differences. The EGSS score=4 subgroup had significantly greater improvements with tazarotene 0.045% lotion ($P<0.05$ versus vehicle lotion) in 3 role-social items (meeting new people, going out in public, and interacting with the opposite sex or same sex if applicable), none of which were statistically significant in the EGSS score=3 subgroup. Mean improvements for the acne symptoms domain was significantly greater for tazarotene 0.045% lotion in the EGSS score=3 subgroup ($P<0.05$ vs vehicle lotion) but not the EGSS score=4 subgroup. Moreover, acne symptoms items that were significant the EGSS score=3 subgroup (bumps on face, bumps full of pus, concerned with scarring) were different from those that were significant in the EGSS score=4 subgroup (scabbing from acne, oily skin). Together, these results suggest that patients with either moderate or severe acne symptoms will likely experience improved quality of life with tazarotene 0.045% lotion. However, patients with more severe symptoms may have greater concerns about social situations and may differ as to which acne symptoms have negative effects on quality of life than those with moderate symptoms.

It was expected that segregating the pooled ITT population by the median Acne-QoL total score at baseline would show greater improvements in the subgroup with worse quality of life (total score <60). However, the magnitude of difference between these participants and those with better quality of life (total score ≥60) was somewhat surprising. No statistical testing was conducted between the Acne-QoL subgroups, but mean improvements in all 4 domains were markedly different between subgroups (score <60 vs ≥60): self-perception (12.1 vs 3.0); role-emotional (10.1 vs 2.0); role-social (8.2 vs 1.2); acne symptoms (9.2 vs 3.7; Figure 3). Some participants in the Acne-QoL score ≥60 subgroup might have experienced a ceiling effect (ie, domain score improved to the maximum possible score), but mean scores at week 12 in this subgroup were below the maximum possible score in all 4 domains (mean, maximum): self-perception (25.5, 30); role-emotional (24.3, 30); role-social (22.1, 24); acne symptoms (22.0, 30); data for mean scores at week 12 not shown in figures.

Both Acne-QoL subgroups had significantly greater improvements with tazarotene 0.045% lotion in the acne symptoms domain and in 2 acne symptoms items (bumps on face, bumps full of pus; $P<0.05$ vs vehicle lotion). However, the Acne-QoL score <60 subgroup had significant improvements with tazarotene 0.045% lotion in 4 additional items (not looking my best, meeting new people, interacting with the opposite sex, concerned with scarring) that were not significant in the Acne-QoL score ≥60 subgroup. In conjunction with the Acne-QoL domain results, these findings strongly suggest that in patients who report poor quality of life due to acne, evaluations should not be limited to clinical assessments of lesions and skin condition. For these patients, issues of social and emotional wellbeing may be equally important, and it is critical to understand whether improvements in the physical symptoms of acne are coinciding with quality-of-life improvements.

Other studies have shown the negative impact of acne on quality life in female and non-White patients.[11-13] Therefore, demographic factors may also need to be considered when assessing quality of life in patients with moderate-to-severe acne. At baseline in participants who were randomized to tazarotene 0.045%, the Acne-QoL subgroup with worse quality of life (score <60) had a higher percentage of participants who were female or Black versus those with better quality of life (score ≥60): female (81.8% vs 50.9%); Black (19.2% vs 11.8%). In addition, results from the exploratory analyses indicated greater improvements for females versus males in all 4 Acne-QoL domains, with the largest differences in self-perception (9.2 vs 4.3) and role-emotional (7.6 vs 2.9). Black participants also had greater mean improvements versus White participants in all 4 domains, particularly in the domains of self-perception (10.3 vs 7.2) and role-social (7.2 vs 4.4). Given the clinical improvements that have been demonstrated in both of these subgroups,[14,15] tazarotene 0.045% lotion may be an attractive treatment option for female and/or Black patients who express negative feelings about their appearance, self-confidence, or ability/willingness to socialize.

These post hoc analyses are limited by the study designs. Acne-QoL was not a primary endpoint in either study, with no Acne-QoL criteria required for eligibility. In addition, the studies were limited to patients with moderate-to-severe acne and therefore, the results of this post hoc analysis may not be gen-

eralizable to patients with mild acne. Moreover, since <10% of participants had an EGSS rating of "severe" at baseline, results from the EGSS score=4 subgroup should be interpreted with some caution.

CONCLUSION

Data pooled from two phase 3 studies indicate that patients with moderate-to-severe acne experienced quality-of-life improvements after 12 weeks of treatment with tazarotene 0.045% lotion. Acne-QoL outcomes appeared to be less affected by clinician-rated acne severity than by participants' own assessments of their quality of life, which tended to be worse in female and Black participants. However, the subgroup with worse quality of life at baseline also had the largest mean Acne-QoL improvements, highlighting the importance of asking patients how acne affects their everyday lives.

DISCLOSURES

Leon Kircik, Edward Lain, and Michael Gold have all acted as investigator, advisor, speaker, and consultant for Ortho Dermatologics. Bruce Katz has nothing to disclose. Hilary Baldwin has served as an advisor, investigator, and on speakers' bureaus for Almiral, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharmaceuticals. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Anya Loncaric and Radhakrishnan Pillai are employees of Bausch Health US, LLC and may hold stock and/or stock options in its parent company.

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AUTHOR CORRESPONDENCE

Leon H. Kircik MD
E-mail:..... wedoderm@yahoo.com

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Tirbanibulin Ointment 1% as a Novel Treatment for Actinic Keratosis: Phase 1 and 2 Results

Steven Kempers MD,[a] Janet DuBois MD,[b] Seth Forman MD,[c] Amy Poon BS MA,[d] Eva Cutler BS BA,[d] Hui Wang PhD,[d] David L. Cutler MD FRCP(C),[d] Jane Fang MD,[d] Rudolf Kwan MBBS MRCP[d]

[a]Minnesota Clinical Study Center, New Brighton, MN
[b]DermResearch, Austin, TX
[c]ForCare Medical Center, Tampa, FL
[d]Athenex, Inc., Buffalo, NY

ABSTRACT

Background: Current field-directed treatments of actinic keratosis (AK), a pre-malignant condition, are often limited by severe local reactions and/or complex treatment. Tirbanibulin, a novel potent anti-proliferative synthetic agent that inhibits tubulin polymerization and Src kinase signalling, is being developed as a convenient, safe, and effective field treatment of actinic keratosis.

Hypothesis: A short course of tirbanibulin ointment 1% safely reduces AK lesions.

Methods: In the Phase 1 study, 4 treatment cohorts with forearm lesions received tirbanibulin ointment 1% over 25 or 100 cm^2 once daily for 3 or 5 days and were evaluated through day 45. In the Phase 2 study, 2 treatment cohorts with face or scalp lesions received tirbanibulin ointment 1% once daily for 3 or 5 days over 25 cm^2 and were evaluated through day 57. Lesion reductions, clearance rates, safety, and pharmacokinetics were assessed.

Results: Forearm AK lesions were reduced by day 45 in all Phase 1 cohorts (N=30). Complete AK clearance at day 57 for face/scalp AK lesions in Phase 2 cohorts (N=168) was demonstrated in 43% and 32% of participants of the 5-day and 3-day cohorts, respectively. Adverse reactions were mainly transient mild local erythema and flaking/scaling, pruritus, and pain. Tirbanibulin plasma concentrations were low or undetectable.

Conclusion: Tirbanibulin ointment 1% was well tolerated and active in AK reduction. Based on activity, the 5-day regimen was selected for Phase 3 development.

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INTRODUCTION

Actinic keratosis (AK) is a pre-malignant condition, associated with prolonged ultraviolet damage predominantly on the face/scalp, trunk, and extremities.[1,2] AK affects ~58 million individuals in the US,[3] and typically occurs in males, fair-skinned individuals, and those of advancing age.[4,5] As the progression of AK to invasive squamous cell carcinoma (iSCC) is unpredictable, the generally accepted approach is to treat all AK.[6] Current treatments are lesion- or field-directed therapies.[1] Lesion-directed therapies are used when the lesion burden is low; but these modalities can cause scarring and long-term pigmentary changes.[1,7] Field-directed therapies are used to treat multiple lesions, large areas, and subclinical lesions.[1,7] Commonly used topical treatments, while effective, frequently cause moderate-to-severe application-site reactions and deleterious effects on uninvolved skin,[7-11] which are often considered unacceptable to patients. Moreover, many of these treatments have lengthy or cumbersome dosing regimens that may undermine treatment compliance and compromise efficacy.[12,13] Given the disadvantages of available topical therapies, there is a need to develop an agent that has low potential for severe local reactions, effective AK clearance, and convenient dosing.

Tirbanibulin is a synthetic, first-in-class, potent anti-proliferative agent that inhibits tubulin polymerization and disrupts Src kinase signaling[14] that are upregulated in AK and iSCC.[15-17] Tirbanibulin also promotes the induction of p53, G2/M arrest of proliferating cell populations, and subsequent apoptosis via stimulation of caspase-3 and poly (ADP-ribose) polymerase cleavage.[14] In vitro, tirbanibulin demonstrated potent inhibition of the growth of primary human keratinocytes and several melanoma cell lines (GI50 ≤50 nM).[14] Preclinical in vitro and in vivo toxicity and dermal irritation studies also supported the further development of tirbanibulin ointment 1% in clinical trials (unpublished data). We hypothesized that a short course of tirbanibulin ointment 1% would be locally safe and active in clearing AK through its mechanism of action that promotes anti-proliferative and pro-apoptotic effects on the actively dividing dysplastic keratinocytes. Here, we describe the results of two early-phase studies in testing this hypothesis.

METHODS

Study Designs and Participants

The Phase 1 study was an open-label, proof-of-concept, single-center study in adults (aged ≥18 years) with clinically typical AK on the forearm. Participants were enrolled into 4 sequential cohorts: Cohort 1 received tirbanibulin ointment 1% 50 mg/day once daily for 3 days over 25 cm^2 treatment area with 4–8 AK lesions; Cohort 2 received 200 mg/day once daily for 3 days over 100 cm^2 treatment area with 8–16 AK lesions; Cohort 3 and Cohort 4 were similar to Cohort 1 and Cohort 2, respectively, but treatment was for 5 days. The Follow-up period was through day 45.

The Phase 2 study was an open-label, uncontrolled, dose-regimen-finding, multicenter study in adults (aged ≥18 years) with clinically typical AK on the face or scalp. Participants were sequentially enrolled and received tirbanibulin ointment 1% once daily for 3 or 5 days over 25 cm^2 treatment area with 4–8 AK lesions; approximately 50 mg/day per application. Response assessment was through day 57 and the Recurrence Follow-up Period was up to 12 months after day 57 for participants who achieved complete (100%) AK clearance in the treatment area at day 57. In both studies, tirbanibulin ointment 1% was formulated in a base ointment containing propylene glycol and glycerol monostearate.

These studies were conducted in accordance with the Declaration of Helsinki, 2013, the US Code of Federal Regulation, and Good Clinical Practice guidelines. The protocols, informed consent forms, and all other appropriate related documents were submitted and approved by the central Institutional Review Board, Quorum Review IRB, Seattle, WA, USA.

Assessments and Statistical Analyses

To assess activity in the Phase 1 study, AK lesion numbers at baseline, days 10, 17, 31, and 45 were summarized by cohort. Complete (100%) and partial (≥75%) AK clearance rates (defined as the proportion of participants who had 100% and ≥75% reduction in AK lesion counts, respectively, in the treatment area at day 45 compared with baseline) were evaluated for each cohort. No statistical inference was made. Participants missing an AK lesion count at day 45 were considered non-responders.

In the Phase 2 study, AK lesions at days 1 (baseline), 8, 15, 29, and 57 were summarized by cohort at each visit. Based on the number of participants who achieved 100% clearance at day 57, the complete response rate and its corresponding 95% Clopper–Pearson Exact confidence interval (CI) were estimated. AK lesion numbers at each timepoint and change from baseline were summarized by cohort at each visit and in subgroups (age, sex, AK lesion count, weight, skin type, and treatment location). The proportion of participants with partial clearance (≥75%) at day 57 were also analyzed. No statistical inference was made.

Recurrence rates and associated 95% CIs were estimated with the Kaplan-Meier method at each post-day 57 visit (at 3, 6, 9, and 12 months post-day 57) and presented by cohort for participants who achieved 100% clearance at day 57.

For both studies, safety was assessed by recording treatment-emergent adverse events (TEAEs) and their relationship to study drug; serious AEs (SAEs); laboratory evaluation of blood chemistry, hematology, and urine analysis; vital signs and electrocardiograms; and physical examinations at predetermined visits according to study protocols.

For both studies, signs of local skin reactions (LSRs; erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) were assessed by investigators on a 5-point scale (0 [not present], 1 [minimal], 2 [mild], 3 [moderate], or 4 [severe]) at predetermined visits according to protocol.

Blood samples were collected to measure plasma concentrations of tirbanibulin pre-dose and at predetermined timepoints for both cohorts in the Phase 2 study. Plasma concentrations were analyzed using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS, lower limit of detection of 0.1 ng/mL).

RESULTS

Participant Populations

In the Phase 1 study, 30 participants were enrolled in one US site. Twenty-nine completed the study and one participant (Cohort 2) withdrew consent on day 2. All 168 participants (n=84 in each cohort) enrolled in the Phase 2 study, from 16 sites across the US, completed the treatment (100% compliance) and follow-up until day 57. Baseline characteristics of all participants met with protocol requirements and were comparable across treatment cohorts, except there were more participants with face than scalp AK lesions in the 3-day vs 5-day cohort in the Phase 2 study. The majority of participants in both studies were White, mean age >60 years, and of non-Hispanic ethnicity with Fitzpatrick skin type I–III (Table 1).

Activity

In the Phase 1 study, reductions in lesion counts from day 1 to 45 were observed in all cohorts (Figure 1). By day 45, 25%, 0%, 50%, and 12.5% of participants demonstrated 100% AK clearance in the treatment area in Cohorts 1–4, respectively (Table 2).

In the Phase 2 study, substantial overall AK clearance on the face or scalp was demonstrated in both cohorts. More participants had 100% clearance at day 57 in the 5-day vs the 3-day cohort (43% vs 32%) (Table 2). Partial clearance rates were also slightly higher in the 5-day vs the 3-day cohort (56% vs 52%) (Table 2). There was a consistent decrease in lesion counts across all visits from baseline to day 57, for both cohorts. A substantial overall mean (standard deviation) decrease from baseline in lesion

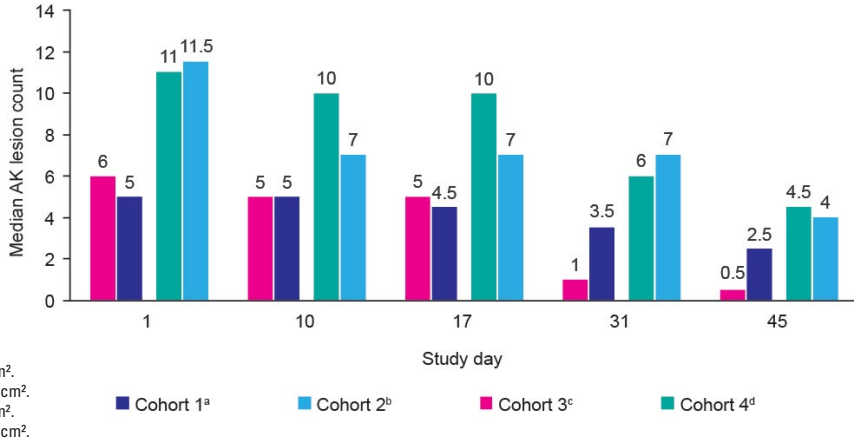
TABLE 1.

Demographic and Baseline Characteristics of Participants from the Phase 1 and Phase 2 Studies

	Phase 1 Study					Phase 2 Study		
	Cohort 1[b] (n = 4)	Cohort 2[c] (n = 10)	Cohort 3[d] (n = 8)	Cohort 4[e] (n = 8)	Overall (N= 30)	5-day cohort[d] (n = 84)	3-day cohort[b] (n = 84)	Overall (N = 168)
Age (years)								
Mean (SD)	63.0 (6.5)	61.8 (8.2)	63.0 (8.6)	64.9 (7.5)	63.1 (7.6)	69.0 (8.9)	67.7 (8.3)	68.3 (8.6)
Sex, n (%)								
Male	3 (75)	6 (60)	5 (63)	5 (63)	19 (63)	76 (90)	72 (86)	148 (88)
Female	1 (25)	4 (40)	3 (38)	3 (38)	11 (37)	8 (10)	12 (14)	20 (12)
Race, n (%)								
White	4 (100)	9 (9)	8 (100)	8 (100)	29 (97)	84 (100)	83 (99)	167 (99)
Other	0 (0)	1 (10)	0 (0)	0 (0)	1 (3)	0	1 (1)	1 (1)
Ethnicity, n (%)								
Hispanic or Latino	0	0	0	0	0	3 (4)	9 (11)	12 (7)
Not Hispanic or Latino	4 (100)	10 (100)	8 (100)	8 (100)	30 (100)	81 (96)	75 (89)	156 (93)
AK lesion count at baseline								
Mean (SD)	4.8 (0.5)	11.9 (2.6)	5.6 (0.5)	11.5 (2.1)	9.2 (3.7)	5.8 (1.4)	5.4 (1.2)	5.6 (1.3)
Median	5.0	11.5	6.0	11.0	10.0	6.0	5.0	5.0
Min, Max	4, 5	8, 16	5, 6	10, 16	4, 16	4, 8	4, 8	4, 8
Location of treatment area, n (%)								
Face						44 (52)	66 (79)	110 (65)
Scalp						40 (48)	18 (21)	58 (35)
Fitzpatrick skin type[a], n (%)								
Type I						11 (13)	13 (15)	24 (14)
Type II						39 (46)	39 (46)	78 (46)
Type III						26 (31)	29 (35)	55 (33)
Type IV						7 (8)	3 (4)	10 (6)
Type V						1 (1)	0	1 (1)
Type VI						0	0	0

AK, actinic keratosis; Max, maximum; Min, minimum; SD, standard deviation.
[a]The Fitzpatrick skin type classification system ranges from very fair (Type I) to very dark (Type VI). Data not collected for Phase 1 study.
[b]50 mg once-daily for 3 days over 25 cm².
[c]200 mg once-daily for 3 days over 100 cm².
[d]50 mg once-daily for 5 days over 25 cm².
[e]200 mg once-daily for 5 days over 100 cm².

FIGURE 1. Median AK lesion count by cohort and visit in participants treated with tirbanibulin ointment 1% in the Phase 1 study.



AK, actinic keratosis.
[a]50 mg once-daily for 3 days over 25 cm².
[b]200 mg once-daily for 3 days over 100 cm².
[c]50 mg once-daily for 5 days over 25 cm².
[d]200 mg once-daily for 5 days over 100 cm².

TABLE 2.

AK Clearance Rate at Day 45 in the Phase 1 Study and Day 57 in the Phase 2 Study in Participants Treated With Tirbanibulin Ointment 1%		
Phase 1 Study	**100% Clearance n (%)**	**≥75% Clearance n (%)**
Cohort 1: 50 mg once-daily for 3 days over 25 cm^2 (n = 4)	1 (25)	2 (50)
Cohort 2: 200 mg once-daily for 3 days over 100 cm^2 (n = 10)	0	3 (30)
Cohort 3: 50 mg once-daily for 5 days over 25 cm^2 (n = 8)	4 (50)	5 (63)
Cohort 4: 200 mg once-daily for 5 days over 100 cm^2 (n = 8)	1 (12.5)	4 (50)
Phase 2 Study	**100% Clearance Proportion of Participants (95% CI)**	**≥75% Clearance Proportion of Participants (95% CI)**
5-day cohort: 50 mg once-daily for 5 days over 25 cm^2 (n = 84)	0.43 (0.32, 0.54)	0.56 (0.45, 0.67)
3-day cohort: 50 mg once-daily for 3 days over 25 cm^2 (n = 84)	0.32 (0.22, 0.43)	0.52 (0.41, 0.63)

CI, confidence interval.

counts occurred by day 15 in the 5-day (-2.5 [2.48]) and 3-day cohorts (-2.5 [2.22]) that continued up to day 57 (-3.9 [2.00] and -3.4 [1.75], respectively) (Figure 2) . Even with small participant numbers, consistency in AK clearance among subgroups was noted.

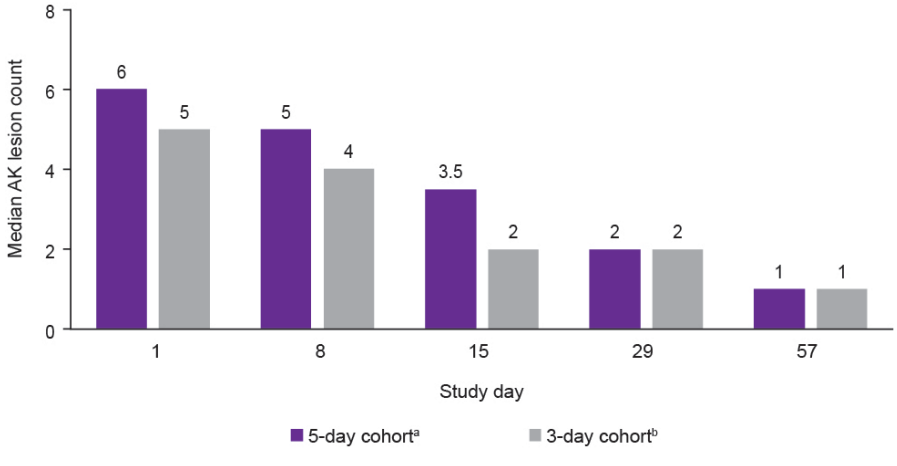
All 63 participants who had 100% clearance at day 57 in the Phase 2 study were included in the Recurrence Follow-up Set. Based on Kaplan-Meier analysis, at 12 months post-day 57, recurrence rates for the proportion of 5 day cohort participants were lower than the 3-day cohort (57% [95% CI, 41, 73] vs 70% [95% CI, 51, 87]). Most recurrence occurred within 6 months post-day 57.

Safety

In the Phase 1 study, no TEAEs were treatment-related, severe, or resulted in withdrawal from the study or treatment. There were no deaths or SAEs. No clinically significant changes in laboratory tests, vital signs, physical examinations, or electrocardiograms were reported. Application-site symptoms, collected separately from AEs, were mostly transient mild pruritus, and less frequently stinging/burning sensation. These were observed predominantly in Cohorts 3/4; all resolved without treatment.

In the Phase 2 study, all participants completed treatment and follow-up to day 57, and both regimens were well tolerated. There were no deaths, SAEs, or discontinuations due to treatment. Twelve of 168 participants (7%) had treatment-related AEs: 9 (11%) in the 5-day cohort and 3 (4%) in the 3-day cohort. Treatment-related AEs were mostly mild, transient application-site pruritus and application-site pain that resolved spontaneously. Three participants reported four treatment-related non-specific systemic AEs: transient mild-to-moderate dizziness and mild headache. One participant reported mild hair darkening near the treatment area, and another was

FIGURE 2. Median AK lesion count by cohort and visit in participants treated with tirbanibulin ointment 1% in the Phase 2 study.



AK, actinic keratosis.
[a]50 mg once-daily for 5 days over 25 cm^2.
[b]50 mg once-daily for 3 days over 25 cm^2.

TABLE 3.

Overview Of Adverse Events (AEs) and Treatment-Related AEs Prior to the Recurrence Follow-up Period in the Phase 2 Study

n (%)	5-day Cohort[c] (n = 84)	3-day Cohort[d] (n = 84)	Overall (N = 168)
AEs	35 (42)	21 (25)	56 (33)
TEAEs[a]	34 (40)	18 (21)	52 (31)
Treatment-related AEs[b]	9 (11)	3 (4)	12 (7)
SAEs	2 (2)	2 (2)	4 (2)
Severe AEs	1 (1)	2 (2)	3 (2)
AEs leading to treatment discontinuation	**0**	**0**	**0**
Deaths	**0**	**0**	**0**
Treatment-related AEs[b]			
Application site pruritus	5 (6)	1 (1)	6 (4)
Application site pain	3 (4)	2 (2)	5 (3)
Dizziness	2 (2)	0	2 (1)
Headache	1 (1)	1 (1)	2 (1)
Hair color changes	1 (1)	**0**	1 (1)
Overdose	1 (1)	**0**	1 (1)

AEs are coded with Medical Dictionary for Regulatory Activities. v18.1. SAEs, serious adverse events
[a]TEAEs are treatment-emergent adverse events that started on or after the first dose or that worsened after the first dose.
[b]Treatment-related AEs are those events considered definitely, probably, or possibly related to study treatment or of an unknown relationship to study treatment.
[c]50 mg once-daily tirbanibulin ointment 1% for 5 days over 25 cm^2.
[d]50 mg once-daily tirbanibulin ointment 1% for 3 days over 25 cm^2.

inadvertently given 10 times the assigned dose but did not report any other AEs or excessive LSRs (Table 3). Concurrent plasma concentrations were undetectable or <0.5 ng/mL. Results of laboratory evaluations, physical examinations, vital signs, and electrocardiograms were within expectations for an elderly population and were unrelated to treatment. From the Recurrence Follow-up Period, there were no treatment-related AEs or skin cancer in the treatment area.

Local Skin Reactions

LSR signs in the Phase 1 study were mostly mild-to-moderate erythema and flaking/scaling, generally appearing on day 4 and peaking ~days 5 or 8 (Cohorts 1/2) and ~days 8 or 10 (Cohorts 3/4), before spontaneously resolving/stabilizing within ~2 weeks. No participants experienced vesiculation/pustulation. No LSR required treatment.

In the Phase 2 study, even though LSRs were frequently observed with tirbanibulin ointment 1%, these were generally minimal/mild (Grade 1/2) erythema and flaking/scaling, were transient, and required no intervention. Less frequently reported were moderate (Grade 3) erythema and flaking/scaling, and minimal/mild (Grade 1/2) crusting. Only one participant (5-day cohort) had transient, severe erythema and flaking/scaling that

TABLE 4.

Maximal post-Baseline LSRs by Grade in Participants Treated With Tirbanibulin Ointment 1% in the Phase 2 Study (N = 84 per Cohort)

	Erythema		Flaking/scaling		Crusting		Swelling		Vesicula-tion/ pustulation		Erosion/ ulceration	
Cohort	5-day[a] n (%)	3-day[b] n (%)	5-day n (%)	3-day n (%)	5-day n (%)	3-day n (%)	5-day n (%)	3-day n (%)	5-day n (%)	3-day n (%)	5-day n (%)	3-day n (%)
LSR Grade												
0	9 (11)	15 (18)	23 (27)	20 (24)	49 (58)	53 (63)	66 (79)	76 (90)	80 (95)	83 (99)	71 (85)	78 (93)
1	22 (26)	34 (40)	20 (24)	33 (39)	27 (32)	20 (24)	16 (19)	8 (10)	4 (5)	**0**	12 (14)	6 (7)
2	35 (42)	29 (35)	24 (29)	23 (27)	8 (10)	10 (12)	1 (1)	**0**	**0**	1 (1)	1 (1)	**0**
3	17 (20)	6 (7)	16 (19)	8 (10)	**0**	1 (1)	1 (1)	**0**	**0**	**0**	**0**	**0**
4	1 (1)	**0**	1 (1)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

LSR, local skin reaction; n, number of participants with LSR; %, percentages are based on the number of participants dosed, 84 per cohort.
LSR rated for each category on a 5-point scale of 0 = none, 1 = minimal, 2 = mild, 3 = moderate or 4 = severe.
[a]50 mg once-daily for 5 days over 25 cm^2.
[b]50 mg once-daily for 3 days over 25 cm^2.

resolved. Few participants experienced erosions/ulcerations or vesiculation/pustulation and none were greater than mild (Grade 2) in severity. In both cohorts, LSRs began by day 2, peaked by the end of treatment, and returned to baseline or resolved by day 29. Slightly more participants in the 5-day cohort experienced LSRs compared with the 3-day cohort. Maximal post-baseline LSR grades are provided to show the highest LSR grade assessed by the investigators regardless of visit in Table 4. Representative photographs of typical and maximal LSRs for both studies are presented in Figure 3.

Pharmacokinetics

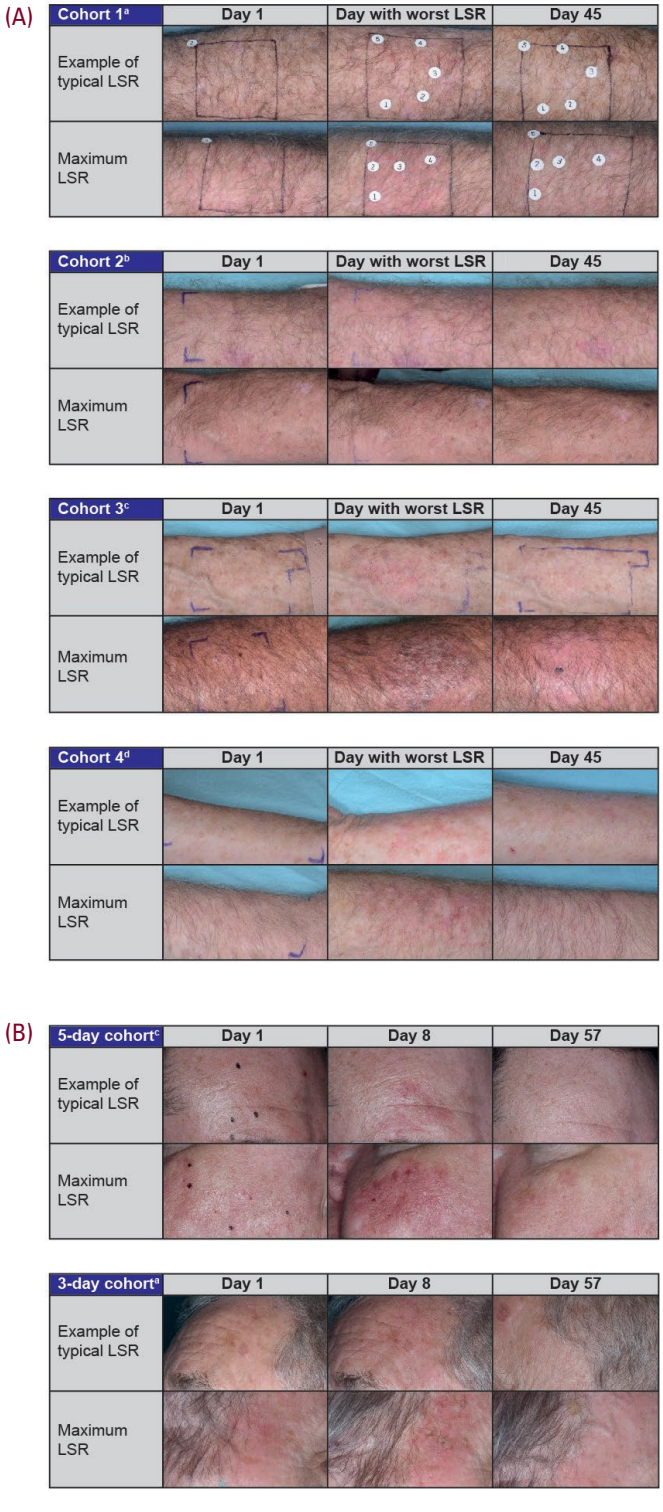
Phase 2 study results demonstrated that tirbanibulin was minimally absorbed following 3 or 5 consecutive days of treatment. For the majority of plasma samples collected, tirbanibulin was below the lower limit of quantification of 0.1 ng/mL. The maximum individual plasma concentration across both cohorts and all days of pharmacokinetics sampling did not surpass 2 ng/mL.

DISCUSSION

AK is very common and a major health concern due to its progression to non-melanoma skin cancers such as iSCC.[6,14,18] Treatment is generally encouraged as predicting which AK lesion will become cancerous is difficult.[6] Commonly used topical therapies include 5-fluorouracil, that is a cytotoxic agent, imiquimod, that acts by immunomodulation, and ingenol mebutate, that induces cell necrosis and inflammation.[8-10] These treatments often lead to moderate-to-severe application-site reactions or LSRs (itching, burning, erythema, flaking/crusting, edema, induration, excoriation, erosion, and ulceration),[8-10] and negatively impact treatment compliance and patients' quality of life.[5,19] Additionally, 5-fluorouracil (twice daily for 2–4 weeks) and imiquimod (twice weekly for ≤16 weeks) require long treatment durations,[8,9] which may prolong patient discomfort from local adverse reactions at both AK lesions and uninvolved areas. Thus, development of an effective and more tolerable topical AK treatment of short duration, having a new targeted mechanism of action, is needed to improve compliance that may lead to better treatment outcomes.

Tirbanibulin ointment 1% is a topical formulation of a novel synthetic molecule that has potent antiproliferative activity against keratinocyte growth in vitro based on inhibition of tubulin polymerization and Src kinase signalling. The reported studies were early-phase development of tirbanibulin ointment 1% in AK among participants with typical demographics and disease characteristics of the target population. Collectively, these studies showed that, firstly, short courses of tirbanibulin ointment 1% are active in reducing AK lesions in multiple locations. Secondly, the low incidence of severe local reactions may serve to differentiate tirbanibulin ointment from other topical treatments for AK. Lastly, these studies supported the

FIGURE 3. Representative photographs of typical and maximum LSRs in tirbanibulin treated participants in (A) Cohorts 1–4 from Phase 1 study and (B) 5-day and 3-day cohorts from Phase 2 study.



LSR, local skin reaction.
[a]50 mg once-daily for 3 days over 25 cm^2.
[b]200 mg once-daily for 3 days over 100 cm^2.
[c]50 mg once-daily for 5 days over 25 cm^2.
[d]200 mg once-daily for 5 days over 100 cm^2.

further development of the 5-day regimen of tirbanibulin ointment 1% in treating AK on the face or scalp in Phase 3 studies.

The Phase 1 study was a proof-of-concept study with a dose-escalating design in treatment area and treatment duration on the dorsal forearm. AK lesion count was consistently reduced in all cohorts, with the 5-day regimen over 25 cm^2 showing the highest complete clearance rate. This 5-day regimen was further evaluated on the face or scalp in the Phase 2 study. Results of the Phase 2 study showed that both 3-day and 5-day regimens had substantial activity against AK, with the 5-day regimen demonstrating numerically higher 100% clearance (43% vs 32%) and sustained response at 12 months post-day 57 (43% vs 30%) than the 3-day regimen. Although both studies were small and uncontrolled, complete AK clearance rates of tirbanibulin ointment 1% at day 57 for the 5-day regimen over 25 cm^2 on the face/scalp or dorsal forearm align well with topical treatment like ingenol mebutate (face/scalp, 42%; trunk/extremities, 32%) administered over 2-3 days.[20]

The favorable safety profile of tirbanibulin ointment was supported by the paucity of systemic, severe, or serious side effects and minimal systemic absorption. Although tirbanibulin ointment did cause some local irritation, it induced mostly mild and transient erythema, flaking/scaling, pruritus, and pain that resolved quickly and spontaneously. The low incidence of severe LSRs and LSRs of greater concern (vesiculation/pustulation and erosions/ulceration) that distinguishes tirbanibulin ointment 1% from other approved topical AK treatments warrant evaluation in future studies.

In summary, these Phase 1/2 studies supported our hypothesis that tirbanibulin ointment 1%, given as a short, once-daily treatment for AK lesions on the forearm, face, or scalp, could reduce lesions and is well tolerated with low-grade LSRs that quickly resolve without intervention. This allowed the 5-day treatment regimen of tirbanibulin ointment 1% to be selected for efficacy and safety evaluation in two double-blinded, placebo-controlled, randomized, parallel-group, multicenter, Phase 3 trials for AK on the face/scalp.

DISCLOSURES

Steven Kempers has no conflicts of interests to disclose.
Janet DuBois has received investigator fees for her institution from Aclaris Therapeutics, Inc., Allergan, Inc., BioPharmX, Botanix Pharmaceuticals, Brickell Biotech, Inc., Cara Therapeutics, Dermata Therapeutics, Dermavant Sciences, Dermira, Inc., Dr Reddy's Laboratories, Endo International plc., Escalier Biosciences, Foamix Pharmaceuticals Ltd., Galderma, GlaxoSmithKline, Glenmark Generics Inc., LEO Laboratories Ltd., Moberg Pharma North America LLC, MOE Medical Devices LLC, Novan, Inc., Perrigo Company plc, Pfizer Inc., Naked Biome Inc., Novartis Pharmaceuticals Corp., SeegPharm SA, Sienna Biopharmaceuticals, Inc., Sol-Gel Technologies Ltd., Taro Pharmaceutical Industries Ltd., Therapeutics Inc., and Valeant Pharmaceuticals North America LLC.
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Amy Poon is a former employee of Athenex, Inc., and may own stock/stock options in Athenex, Inc.
Eva Cutler is an employee of Athenex, Inc.
Hui Wang is an employee of Athenex, Inc., and may own stock/stock options in Athenex, Inc.
David Cutler is an employee of Athenex, Inc., and may own stock/stock options in Athenex, Inc.
Jane Fang is a consultant of Athenex, Inc., and may own stock/stock options in Athenex, Inc.
Rudolf Kwan is an employee of Athenex, Inc., and may own stock/stock options in Athenex, Inc.

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AUTHOR CORRESPONDENCE

Jane Fang MD
E-mail:..... jfang@athenex.com

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ORIGINAL ARTICLE

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Therapies for Psoriasis: Clinical and Economic Comparisons

Albert Marchetti MD,[a] Tina Bhutani MD,[b] Benjamin Lockshin MD,[c] Daniel M. Siegel MD,[d] Frederick Behringer MD[e]

[a]Med-ERA, Inc., New York, NY; Rutgers New Jersey Medical School, Newark, NJ

[b]Psoriasis & Skin Treatment Center; Dermatology Clinical Research Unit, University of California, San Francisco, CA

[c]Clinical Trials Center; Derm Associates, Silver Spring, MD

[d]SUNY Downstate and Brooklyn Veterans Administration, New York, NY

[e]Suncoast Skin Solutions, Ocala, FL

ABSTRACT

Background: Clinical and economic comparisons of therapies for plaque psoriasis are regularly updated following each new development in the field. With the recent availability of a novel accessory (Multi Micro Dose™ [MMD®] tip) for the 308nm excimer laser (XTRAC®, Strata Skin Sciences, Horsham, PA), which can determine and deliver an optimal therapeutic dose (OTD™) of ultraviolet-B light in an improved protocol, the need for comparative health-economic assessment recurs. To this end, a comprehensive evaluation of treatment-related costs was undertaken from the payer perspective. Results show that outcomes are influenced by many factors; most importantly, the severity and extent of disease, treatment selection, and patient preference, as well as compliance, adherence, and persistence with care. Among study comparators, the 308nm excimer laser – XTRAC – with its latest MMD enhancement, is safe and delivers incremental clinical benefits with the potential for significant cost savings. These benefits are particularly relevant today in the context of SARS-CoV-2 virus and the COVid-19 pandemic.

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BACKGROUND

Plaque psoriasis is an immune-mediated chronic inflammatory disease that is physically categorized by raised scaly epidermal plaques. Pathophysiology is yet to be fully elucidated but is described as keratinocyte and vascular hyperplasia with an infiltrate of T-lymphocytes, neutrophils, and various other inflammatory cells into affected regions of epidermis.[1] Immune dysfunction involving the release of cytokines from infiltrated T cells, dendritic cells, resident immune cells and hyperplastic keratinocytes drives pathologic mechanisms.[2]

Approximately 2.2% of Americans has psoriasis.[3] Worldwide, more than 125 million people suffer from the physical and psychologic impact of the disorder.[4]

Millions of psoriasis-related healthcare visits occur annually in the US.[5] Estimated direct medical costs before broad utilization of biologic therapies averaged from hundreds to thousands of dollars/patient/year and were correctly predicted to rise with the expanded use of biologic therapies.[6-8] In 2013 dollars, the total annual healthcare costs related to psoriasis in the U.S. amounted to $112–$135 billion, according to previous economic analyses and assessments from the National Psoriasis Foundation.[9]

Therapy

With treatment, providers seek to reduce the signs and symptoms of disease as measured by reductions in the psoriasis area and severity index (PASI) and/or physician global assessment (PGA) score.[10] Therapeutic selection is dictated initially by severity, extent of disease, and impact on quality of life.[11] Thereafter, the frequency and severity of potential adverse events as well as the likelihood of response, speed of onset, duration of remission, need for maintenance, and affordability of care drive therapeutic decisions. Patient preference must also be considered.[12,13] Finally, providers prefer therapies that are safe, effective, and easy to administer, while payers prefer less costly options. Note: with the advent of COVid-19, some safety concerns have been re-emphasized.

The American Academy of Dermatology treatment guidelines recommend that therapy for mild-to-moderate disease begins with topical corticosteroids, plus/minus other topicals such as calcipotriene or tazarotene, alone or in combination.[14] For more severe, extensive, or recalcitrant disease, phototherapies, oral systemics, or biologics are indicated in this order and may be used solo or in combination with each other and/or topicals.[14]

The real-life utilization of all interventions is variable, as they may be switched, discontinued, restarted, combined, rotated,

or abandoned depending on their tolerability, safety, and effectiveness, as well as patient compliance and satisfaction. According to observational research, the majority of patients never start treatment or abandon first-line therapy, either temporarily or permanently, some without ever achieving a treatment success.[15] This observation speaks to the oft-cited statement that many patients remain dissatisfied, untreated or under-treated, seeking care only during periods of duress or special circumstance.[16-20]

Health Economic Assessment

To assess key economic and clinical aspects of care, a health-economic study was conducted from the payer perspective. Study considerations were: required care days, likelihood of response, speed and completeness of response, frequency and duration of remission, adverse events and their management, resource utilization, and the cost of consumables. Once these items were quantified, monetized, and summed, their costs were compared across comparators.

Objectives

1. To demonstrate the expected annual direct cost associated with XTRAC™ excimer laser in an optimal therapeutic dose protocol (XTRAC OTD™)
2. To compare that cost and associated clinical outcomes with those of comparator therapies.

METHODS

Literature searches were conducted through Embase, PubMed and Ovid Medline for reference articles relating to study objectives. Relevant medical subject headings, used individually and in combinations, directed our searches. Thousands of articles were initially identified and subsequently reduced in number by combining search terms, then examining titles and abstracts for relevance. Other data and information were sought through Yahoo and Google search engines, using similar subject headings. Ultimately, 220 articles were retrieved and reviewed for content and data to inform the study and contribute to an analytic dataset. Association guidelines, randomized controlled registration trials, large systemic reviews, strict meta-analyses, and large database analyses focused our final reference selection and became preferential data sources.

At the same time, an advisory panel of clinical and academic dermatologists was convened to inform the study and review analytic methods, data, results, and conclusions. This process was aided by a survey fielded to each advisor, completed, and returned with recommendations regarding the common use of study comparators in actual clinical practice. Suggestions were also provided to guide modeling concepts and data selection. Advisors also reviewed study results and contributed to the study's final report.

Cost Methodology

The largest segment of patient with psoriasis, approximately 80% to 85% of cases, have mild-to-moderate disease that is limited in severity and distribution across ≤3% body surface area (BSA).[14,21,22] Remaining patients have moderate-to-severe disease composed of thicker, more inflamed and widespread plaques, affecting >3% to 10% BSA in moderate cases and >10% BSA in severe cases. To be comprehensive, all patients who require treatment were considered – those with mild-to-moderate disease who generally start on topical therapy as well as those with moderate-to-severe disease who receive phototherapy, traditional systemics, and biologics, as well.

Full prescribing information,[23] procedural protocols,[24] and clinical guidelines[14,25-27] containing manufacturer and academic recommendations contributed information on approved product use. Observational research[28,29] that reported actual product utilization and therapeutic persistence further informed decisions about annual resource consumption.

According to these sources, regimens of phototherapy are used repeatedly during any year. Other modalities typically are used continuously (methotrexate), interrupted temporarily (super-potent topicals), or scheduled periodically (biologics). These considerations contributed to conceptualized actual care and the resource utilization assigned to each comparator. Taken together, a full year of recommended resource utilization (ideal) adjusted with reported average duration of care (real) directed our projections of resource consumption and costs that formed the lower limit of our economic estimates for an adjusted annual time horizon. However, observational research[30] also reports that some patients stay on treatment for at least 12 months, thereby providing an upper limit of consumption and costs for a full annual time-horizon. In this way, we projected a range of cost outcomes, expressed as 50th and 100th percentiles, for each comparator.

RESULTS

Resource Utilization

Eight comparators – clobetasol and calcipotriene in combination (CLO/CAL), narrow-band UVB (NB-UVB), XTRAC +/- OTD, methotrexate (MTX), etanercept (ETA), infliximab (INF), and ustekinumab (UST) were assessed. Components of annual care assigned to each comparator are shown in Table 1.

Healthcare Days

Based on information in Table 1, a calendar of events was created and used to determine the number of actual healthcare days required to utilize each comparator during one year of ideal care. If two care components could be reasonably delivered on the same day, only one day would accrue to the total (See Figure 1).

TABLE 1.

Comparator Resource Utilization								
	CLO / CAL	NB-UVB	XTRAC	XTRAC-OTD	MTX	ETA	INF	UST
Work Up	H&P	H&P	H&P	H&P	H&P	H&P	H&P	H&P
Dose or Procedures	CLO 0.05% bid for 3wks	tiw for 10 wks Total 30 proc/cycle	biw for 6 wks Total 12/cycle	qw for 5 wks Total 5/cycle	7.5mg qw	50mg biw x 3 mo	5mg/kg qw @ wks 1, 3, 7	45mg sc (pts ≤100kg) qw @ wks 1, 5
Maintenance	CLO tid on weekends, CAL qd on weekdays	bim for 4 mos Total 8 proc/cycle	None	None	7.5mg qw	50mg qw maintenance	5mg/kg q8wks maintenance	45mg q12wks maintenance
Testing	None	None	None	None	7 CBC/Met panels, 1 TB/ HCV/HBV test, chest x-ray, (AEs: 2.5 f/u visits/ AE x 6.3%)	2 CBC/Met panels. 1 each: TB/HCV/ HBV/HIV/ ANA test. Chest x-ray if TB positive. Periodic H/P. Skin ca screen @ MD's discretion. 3/1°, 2/2° visits annually.		
Procedures	None	38/cycle	12/cycle	5/cycle	Liver biopsy as directed by signs/ symptoms x 6.3%	None	None	None
Office Visits (MD) / Cycle	4	4	1	1	10	5	5	5
Cycles/year	2	2	3	3	1	1	1	1
Total care days per year	294d	80d	39d	18d	62d	70d	14d	11d

FIGURE 1. Total expected care days per comparator for 12 months of treatment.

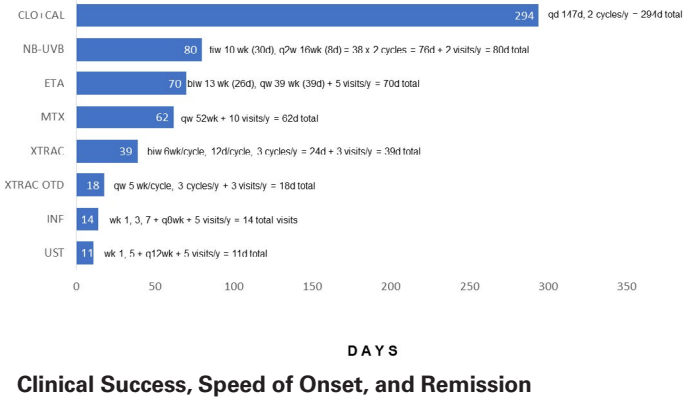
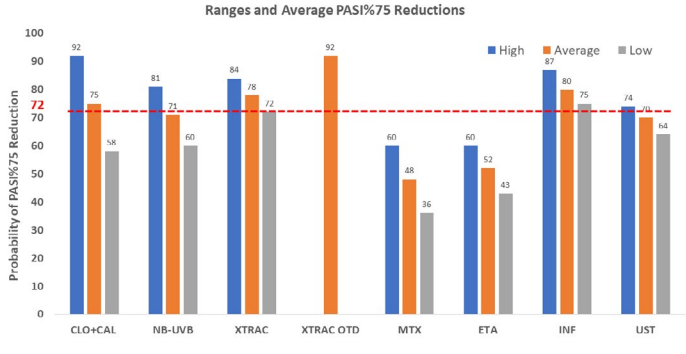


FIGURE 2. Range of commonly reported PASI75 reductions for each comparator.



Clinical Success, Speed of Onset, and Remission

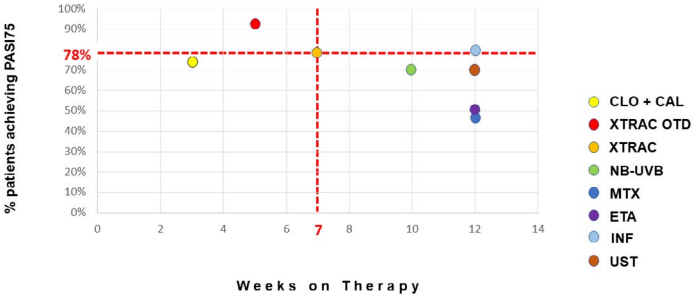
PASI score was the outcome measure selected to represent the effectiveness of study comparators. A decrease of ≥50% from PASI baseline was deemed a clinical response; ≥75% was considered a clinical success and, if maintained, a remission. Following treatment success, a return to <50% improvement in the original PASI baseline score was considered a relapse. Average probabilities of responses and successes used in this study were drawn from cited references and reflect commonly reported ranges. For XTRAC OTD, the only available PASI scores came from its recent clinical trial, which became the value used in our study (See Figure 2).[24]

Another meaningful gauge of clinical effectiveness is time to achieve clinical success (ie, PASI75 reduction), which marks the onset of remission. At this point, treatment cessation is possible, or a modified maintenance phase of therapy can begin or the dosing regimen that initiated remission can be perpetuated as long as safety is sustained. (See Figure 3.)

Safety

Across psoriatic treatments, the potential for serious adverse events is greater with systemic therapies than topicals or light and mandates pretreatment patient evaluations and continuous monitoring during care. These requirements are reflected in

FIGURE 3. Time to achieve clinical success (speed of onset) and the likelihood of that achievement.



resource utilization assigned to each systemic comparator and contributed to their total annual costs. Descriptions of the most common and/or serious adverse events related to each comparator class follow. Specific safety concerns related to SARS-CoV-2 virus and the COVid-19 pandemic are cited in the Discussion.

Super-Potent Topical Steroids

The most common adverse events related to super-potent steroids are telangiectasia, local atrophy, striae/scar extension, rosacea, acne, pigmentation, purpura, cutaneous infections, and delayed healing.[31] Some of these conditions can persist. Moreover, because topical steroids are absorbed transcutaneously, they can interfere with natural steroid production, which can have untoward consequences (Addison crisis).[32] Absorbed steroids can also affect glycemia and diabetes.[33]

Phototherapy

Office-based phototherapies are delivered professionally, so the likelihood of misuse is negligible. Regardless, if an excessive dose is delivered, burning and/or blistering similar to sunburn can occur. With the excimer laser, the extent of injury should be minimal because treatment is directed to specific lesions, not broad surfaces. Management costs are inconsequential.

Traditional Systemics

Unlike topical steroids and phototherapies, methotrexate and other traditional systemics bear numerous safety warnings that mandate close patient monitoring. Some side effects, such as pruritis, nausea, vomiting, diarrhea, headache, rash, dizziness, fatigue, and insomnia are common and usually manageable. Others, like hepatitis, pneumonia and opportunistic infections, as well as malignancies, can be serious, even fatal. Suspicion of pneumonia or hepatitis requires thorough and possibly invasive investigations (eg, transcutaneous biopsy).[25,34,35] (See Table 2). According to a meta-analysis of methotrexate safety data derived from 34 randomized studies of ≥50 patients undergoing treatment ≥12 weeks, 6.9% of methotrexate adverse reactions are treatment-limiting.[36]

TABLE 2.

Methotrexate Safety Monitoring[25]	
Patients without Risk Factors	**Patients with Risk Factors**
Baseline history, physical, CBC, Met panel, hepatitis screen, chest x-ray	Liver biopsy after 6 months of treatment
CBC and platelet count 5-6 days after 1st test dose	Repeat liver biopsy after every accumulated 1.0g-1.5g of drug
BUN, creatinine, liver function tests (LFTs) of albumen, ALT/AST monthly for first 6 months then q 1-3 months there	Pregnancy test and HIV test in selected patients
Liver biopsy only in patients with history or risk of liver disease (ie, abnormal LFTs for 12 months or after every accumulated 3.5g-4.0g of drug)	Repeat chest x-ray if patient has underlying pulmonary disease or develops symptoms, eg, cough
Fibrosis testing may replace biopsy	Consider tuberculosis testing

Biological Systemics

As with traditional systemics, all biologics carry safety risks that require comprehensive pretreatment evaluations and continuous monitoring.[37] Safety concerns, warnings, and recommendations for individual monoclonals vary slightly based on their targeted immune mediators. Newer biologics have limited longitudinal safety data to definitively establish long-term risk.

For tumor necrosis factor alpha (TNFα) inhibitors, available since 2003, long-term safety data have been analyzed. Reports show minor side effects are common and relate predominately to injection-site reactions. On the other hand, severe events are rare but can be wide-ranging.[38,39]They include infections such as pneumonia, tuberculosis, hepatitis, and bacterial infections of listeria and legionella, viral brain infection, and sepsis, as well as cancer, heart failure, and liver dysfunction with failure. Drug labels for TNFα blockers include warnings about these issues that include the following statements:[40]

- Patients treated with TNFα blockers are at increased risk for serious infections involving multiple organ systems that may lead to hospitalization and death.
- Risks and benefits should be considered before treatment in patients with chronic or recurrent infections and/or predisposing conditions.
- Patients ≥65 and those taking concomitant immunosuppressants may be at greater risk.
- Prior and during treatment, patients should be evaluated and tested for tuberculosis and monitored for other serious infection.
- Empiric antifungal therapy should be considered in patients at risk.

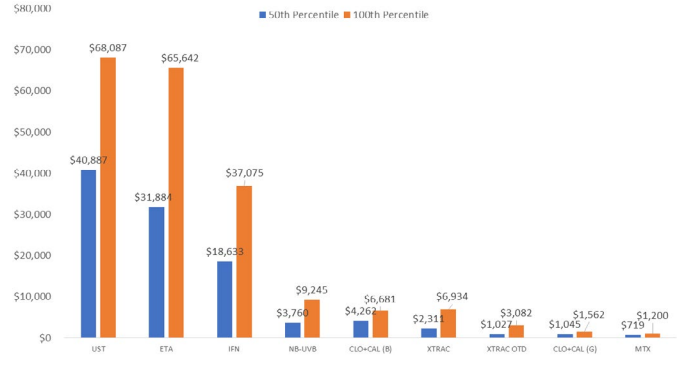
Reactivation of tuberculosis and certain viruses – hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) – are particularly disconcerting and require dedicated

management.[41] The likelihood of cardiac complications or the development of malignancies appears to equate with risks noted among general psoriatic populations treated with other interventions.[38,41-43] For all of these reasons, anti-TNF-a biologics prescribed for psoriasis have been tagged with black-box safety warnings.[40,44]

Annual Costs

Following the identification of 1) the full complement and frequency of resources consumed during the utilization of each comparator, 2) the nature, severity, and frequency of associated adverse events, and 3) the resources required to monitor and manage side effects, a cost was assigned to each consumed component. All costs were then summed to achieve an expected, total annual cost of direct care (real and ideal) for each comparator (See Figure 4).

FIGURE 4. Total expected costs for each comparator during one year of real and ideal care.



DISCUSSION

The study of economics relates to human behavior and the proposition that people innately seek certain goals throughout their lives. Human behavior is purposeful and directed by self-interests that are unlimited and require significant resources to achieve.[45] A basic principle of economics and, by extension, health economics is the notion that all resources are limited and cannot meet unlimited needs or demands.[46]These considerations establish the fundamental issue for health economists; ie, how to best allocate resources to achieve desired objectives and goals when one side of the equation is finite and the other is not? To answer this question, economics is applied to healthcare via theories, models, and analyses that aid decision-making in a myriad of circumstances and environments.[45,46]

Another economic concept is the notion of achieving cost-efficiency with limited resources. Efficiency improvement relates to containing costs and/or improving outcomes, all else being equal, thus demonstrating value.[45,47] These concepts are especially meaningful at the societal level and in the provision of population medicine in capitated systems. To expend costly resources excessively on one patient or a specific group leaves fewer resources and dollars for all others, thereby increasing inequity and compromising the current mandate to expand access.

The current assessment is intended to address these issues and help inform decisions about the care of patients with plaque psoriasis. Results of our study show that outcomes can be improved, and costs can be diminished through the judicious use of individualized therapies with proven benefits at established costs. The least costly therapy in this study is methotrexate (total annual cost, $719– $1,200 per year [50th and 100th percentile projected costs]). This intervention is justified by virtue of cost alone but must be put into perspective by likelihood of response (50% for PASI75), time to remission (14 weeks), need for continuous maintenance, and full 12-month care days (62), as well as vigilance for serious adverse events.

The most expensive comparator in this study is ustekinumab ($40,887 [50th percentile] to $68,087 [100th percentile]). The use of this product is justified by a high likelihood of response (70% PASI75) and the fewest number of required care days (11 days). The onset of remission is prolonged compared to other alternatives, and maintenance is required to sustain response. Ongoing concerns for the development, reactivation, or exacerbation of serious infections accompany clinical use.

Other biologics, etanercept ($31,884–$65,642) and infliximab ($18,633–$37,075), were also found to be costly compared to nonbiologic alternatives. Of the two, infliximab can be expected to deliver a greater likelihood of PASI75 response (65% vs 50% for etanercept) with fewer annual care days (14 vs 70). As with ustekinumab, these two biologics are strapped with the same black box safety warnings and similar requirements for pretreatment evaluation and continuous monitoring. Newer biologics with higher clearance rates still require additional study to identify and quantify safety risks before definitive statements can be made about their long-term value.

Continued sequential use of both clobetasol and calcipotriene is required to maintain clinical success. Two similar cycles with an interim drug-free period for steroid relief constitute annual care in this study. Speed of onset (5 days) is excellent for patients with mild disease. Generic formulations of these two products dominate the market, but branded versions are still being used by some patients. For this reason, two calculations were undertaken to estimate the annual cost for both versions in a similar treatment regimen. Generic annual costs are $1,045–$1,562; branded costs are substantially greater – $4,262–$6,681.

Narrow-band ultraviolet light has expected annual costs of $3,760–$9,245. Safety is not a significant issue, but the inconvenience of ongoing procedures (80) in one year is unacceptable to some patients. Response rates are good (71%

PASI75), but time to remission is prolonged (10 weeks) and maintenance is required to retain the response.

The XTRAC excimer laser with and without its latest innovations delivers rapid responses and sustained remissions without maintenance. Treatments are safe and fewer in number compared to NB-UVB, topicals, and oral systemics. Adverse events are uncommon, except for possible sunburn-like reactions around treatment areas. Of the two XTRAC options, improved XTRAC-OTD can deliver a response that approaches clearance (PASI 92%) with fewer treatment procedures per cycle (5 versus 12) than the previous XTRAC technology in a shorter timeframe (5 versus 6 weeks). The difference in expected annual costs is $2,311–$6,934 versus $1,027–$3,081, respectively, for XTRAC +/- OTD) and reflects three treatment cycles for each full year.

This information is particularly timely in light of the COVid-19 pandemic. All clinical practices have been affected in some way, including dermatology where the use of biologics has been met with increased concern. Patients on biologics, especially those with comorbidities,[48,49] might bear higher risk for more severe SARS-CoV-2 infection. In response to COVid-19, the American Academy of Dermatology,[50] National Psoriasis Foundation/ International Psoriasis Foundation,[51] and the British Association of Dermatologists[52] have issued guidelines that state:

- Psoriasis patients should stop a biologic if they develop SARS-CoV-2 infection.
- Psoriasis patients over the age of 60 and/or patients with comorbid conditions have a higher risk of morbidity and mortality as well as a more complicated recovery.
- The benefit-to-risk ratio of any immunosuppressive therapy should be carefully weighed in these patients on a case-to-case basis.
- Alternative therapeutic approaches can be considered to treat high-risk patients.

Fortunately, there are numerous therapeutic options for patients with psoriasis that not only offer excellent clinical benefits but also can deliver cost savings at a time when national healthcare expenditures have unexpectedly increased. The clinical and cost data compiled in this report can help practitioners select appropriate alternative care for patients currently using a biologic therapy and those with comorbidities, if risk-reward is questioned.

CONCLUSION

The technologic evolution of the XTRAC excimer laser used in an optimal therapeutic dose regimen (XTRAC OTD) translates into substantial clinical and economic benefits for patients with plaque psoriasis – excellent safety, rapid response, high likelihood of PASI75 reductions, potential for clearance (PASI92), relatively few care days, and a cost that is lower than biologics, NB-UVB, previous XTRAC, and possibly even some generic topicals at the lower half (50th percentile) of potential cost outcomes. Collectively, these benefits translate into improved cost efficiency.

Study Limitations

The current study has limitations that are common to similar types of analyses of previously published data: 1) Inputs are derived from published literature and include all limitations therein. 2) discrepancies among referenced studies can influence the current study's results. 3) XTRAC OTD outcomes are based on results from one clinical trial. 4) Treatment persistence is estimated using published observational research and includes all limitations therein. 5) Persistence with phototherapy may be underestimated in longitudinal databases because a hiatus in utilization may result from remission which is indistinguishable from therapeutic abandonment in such databases. 6) Adverse events costs accrue only to payers and are based solely on resources required to identify and manage individual events.

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Dr. Bhutani is currently an investigator for Celgene, Regeneron, and Janssen. She has served as a consultant for Abbvie, Lilly, and Meiji Pharmaceuticals.

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AUTHOR CORRESPONDENCE

Albert Marchetti MD

E-mail:.....albertmarchetti@yahoo.com

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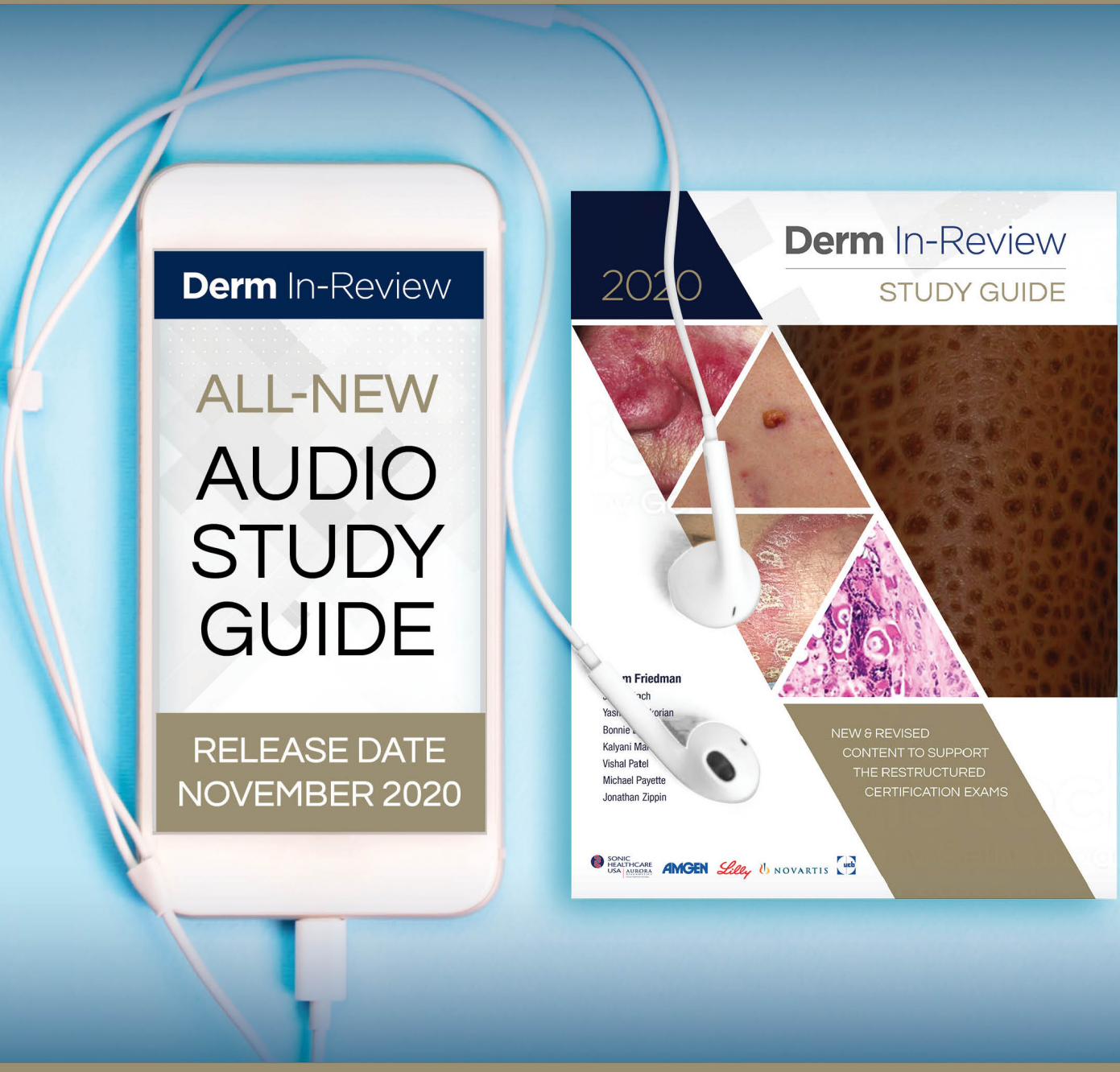

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CASE REPORT

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Rapid Evolution of a Squamous Cell Carcinoma In Situ to Locally Invasive With Perineural Involvement

Margit Juhasz MD MSc,[a] Joel L. Cohen MD[a,b]

[a]University of California, Irvine, Department of Dermatology, Irvine, CA

[b]AboutSkin Dermatology and DermSurgery, Greenwood Village, CO

ABSTRACT

We present a case of rapidly progressing squamous cell carcinoma in situ (SCCis) with progression to aggressive SCC. An elderly gentleman with multiple medical comorbidities presented with a left zygomatic tumor initially diagnosed as SCCis with adnexal extension on histology. After a period of approximately 10 weeks, the patient underwent Mohs micrographic surgery (MMS) with evidence that the tumor was now consistent with a well-differentiated SCC, with perineural involvement. MMS was stopped after two stages and the patient was sent to head and neck surgical oncology for further evaluation and management.

It has been reported in the literature that 3–5% of SCCis will progress to invasive SCC; although the inciting event to cause such progression is unknown, it is thought that mutations in key oncogenes or tumor suppressor genes such as *TP53* may play a role. In addition, as many as 31% of SCCis may have a component of invasive SCC that is missed on initial histology due to sampling bias. This case reminds us that sampling bias can occur during biopsy, SCCis can rarely progress to invasive SCC, and highly aggressive SCCs may prove to be therapeutically challenging requiring a multidisciplinary approach.

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INTRODUCTION

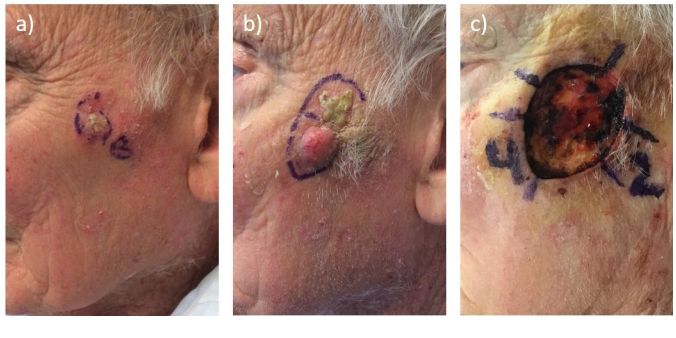
Non-melanoma skin cancers (NMSCs) are one of the most common type of cancer worldwide. When diagnosed early, basal cell and squamous cell carcinomas (BCC and SCC, respectively) are easily treated with local destruction or surgical excision. However, delay in detection or treatment can result in NMSCs becoming locally destructive, invasive and even metastatic. SCC in situ (SCCis, also known as Bowen or Bowen's disease) is a superficial form of SCC in which cancerous cells have not invaded through the full-thickness epidermis. The presence of atypical basaloid cells is associated with progression of pre-cancerous skin lesions to invasive SCC.[1]

There is a reported 3%–5% rate of SCCis progression to invasive SCC;[2] however, occult invasion of SCCis has been reported in as many as 10% of cancers subsequently removed by surgical excision or Mohs micrographic surgery (MMS).[3] Due to sampling bias, it has been reported that 31% of SCCis diagnosed on biopsy can have a component of invasive SCC which is discovered on the final pathology of the surgically excised specimen.[4] In this report, we describe a case of a rapidly progressive SCCis to invasive SCC with perineural involvement resulting in a therapeutic and diagnostic conundrum.

CASE

A 91-year-old man with an extensive medical history including multiple NMSCs, colon cancer, severe heart disease requiring a pacemaker, and multiple orthopedic fractures secondary to osteoporosis presented to clinic with a biopsy-proven SCCis with adnexal extension on the left zygoma. The patient was subsequently scheduled for MMS, however suffered a hip fracture requiring admission to a rehabilitation facility for eight weeks. The patient was offered radiotherapy, however refused, and MMS was scheduled upon patient's discharge from the rehabilitation center. The patient underwent MMS 10 weeks after initial diagnosis of the SCCis.

FIGURE 1. A case of a 91-year-old man with a (a) SCCis at initial biopsy, (b) SCC with perineural invasion at MMS 10 weeks later, and (c) the surgical defect after two stages of MMS. Although the tumor extended deep to the surgical defect, the patient ultimately decided to discontinue treatment and the area was closed with a graft performed by head and neck surgical oncology.



By this time of surgery, the tumor had significantly increased in size to clinically measure 4.7 x 2.3 cm. First layer histology revealed an aggressive, well-differentiated SCC extending deep into fat with perineural involvement. A second layer was taken; given the extensive involvement of the deep tissue, it was decided to stop MMS, consult head and neck surgical oncology, and leave the current surgical defect open, which measured almost 6 cm.

Upon workup, computed tomography (CT) of the head and neck revealed no underlying bony defects or evidence of regional metastatic disease, and although the CT of the chest demonstrated granulomatous disease, there was no evidence of metastatic disease either. Head and neck surgical oncology had a long discussion with the patient and his wife regarding further management of the SCC – watchful waiting, re-excision under general anesthesia with cardiology clearance, or radiotherapy. Given his age, comorbidities, and further risks associated with continued treatment, the patient opted for closure of the surgical site with a delayed skin graft and watchful waiting.

Three months after MMS, the patient presented to his primary care doctor with a well-healed graft site over the left cheek. No local recurrence of the SCC was noted at this time. The patient did not demonstrate evidence of metastatic disease to regional lymph nodes.

DISCUSSION

SCCs arise secondary to clonal expansion of keratinocytes harboring ultraviolet-induced DNA mutations, specifically the *TP53* gene. Further "hits" to keratinocyte DNA affect genes important for cell proliferation, adhesion, and migration causing locally invasive (perineural and/or perivascular), as well as possible metastatic disease. SCCis is an early, superficial carcinoma that can be treated using a multitude of techniques including liquid nitrogen, topical chemotherapeutics, curettage with or without electrodessication, photodynamic therapy, local radiation, laser therapy, and excision. However, with invasion, therapeutic options become limited – depending on the anatomic location, medical practitioners will often favor surgical techniques including wide local excision or Mohs micrographic surgery.[2]

Progression from SCCis to invasive SCC is relatively rare, with a reported 3%–5% conversion rate.[2] Mutations in key oncogenes or tumor suppressor genes may have resulted in the rapid progression of our tumor. Future advancements in whole genome sequencing may allow for characterization of the initial SCCis lesion versus the subsequent SCC to reveal specific DNA mutations associated with an increased risk of invasion and perineural involvement. Given recent developments in molecular characterization of melanomas in the outpatient setting, it is possible that sequencing of NMSCs is right around the corner. It is also possible that sampling bias during the initial biopsy may have contributed to misdiagnosis.[4]

As authors, we feel that this case is important to present to the dermatologic community, as it embodies the therapeutic and diagnostic challenges dermatologic surgeons encounter when faced with an aggressive, invasive carcinoma. Given our tumor's size on presentation for MMS, perineural extension and patient comorbities, this aggressive SCC proved a therapeutic challenge requiring a multidisciplinary approach with input from ENT, head and neck surgical oncology, and radiology. Although ultimately it was decided to discontinue further treatment and close the surgical defect with a graft, in other cases where patients are younger or have less comorbid disease, additional therapy with surgery and/or radiation may be warranted for locally invasive SCC.

DISCLOSURES

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The authors have no relevant conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Margit Juhasz MD

E-mail:..... jmjuhasz@uci.edu

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CASE REPORT

Journal of Drugs in Dermatology

Ablative Fractional Resurfacing for Chronic Wounds from Traumatic Scarring: A Case Report and Literature Review

Joseph N. Mehrabi,[a] Kristen M. Kelly MD[a,b]

[a]University of California, Irvine, CA

[b]Beckman Laser Institute, Laser Microbeam and Medical Program, University of California Irvine, Irvine, CA

ABSTRACT

Ablative fractional resurfacing (AFR) can be utilized to improve scar appearance, texture, pain and associated contractures. Non-healing ulcers can also develop in areas of scarring and, in some cases, AFR can be utilized to heal these chronic wounds. We present a case of scarring with non-healing ulceration refractory to wound care, debridement and hydrotherapy successfully healed in four sessions with AFR using a 2940 nm Er:YAG laser. We review the literature on AFR for wound healing including potential mechanisms. AFR can be considered for non-healing ulcers in areas of scarring, once malignancy and infection are ruled out, and has the potential to provide relief for these suffering patients.

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INTRODUCTION

The efficacy of lasers for scar treatment is well documented and multiple lasers are known to improve scars. Ablative fractional resurfacing (AFR) can be especially beneficial to improve scar appearance, texture, pain and associated contractures.[1] AFR is performed with carbon dioxide (CO_2) and erbium yttrium aluminum garnet (Er:YAG) lasers with water as the target chromophore.

Fractional photothermolysis works by creating columns or microthermal treatment zones (MTZs) of controlled thermal injury with a grid-like pattern at an operator-determined depth and density.[2] The clinician can target the approximate depth of the scar and make depth and density adjustments based on body location as well as scar characteristics. The healthy skin between the MTZs facilitates a rapid wound healing response contributing collagen reconstruction and scar remodeling.[3] The ablated pinholes from AFR also relax skin contractures, promoting improvement, some immediate, in areas of tension.[4,5] The open MTZs also can act as channels for topical drug delivery, which can be used to enhance treatment and achieve less painful more uniform distribution of drugs.[6]

AFR has been established as the first line method for the treatment for traumatic scars in many centers.[7,8] Multiple studies have consistently documented significant subjective and objective improvements in scar appearance, color, height, texture, pliability, restriction, pain and itch, as well as an overall improvement in quality of life.[8] Most experts agree that AFR is the most effective overall laser platform for traumatic scars.[8]

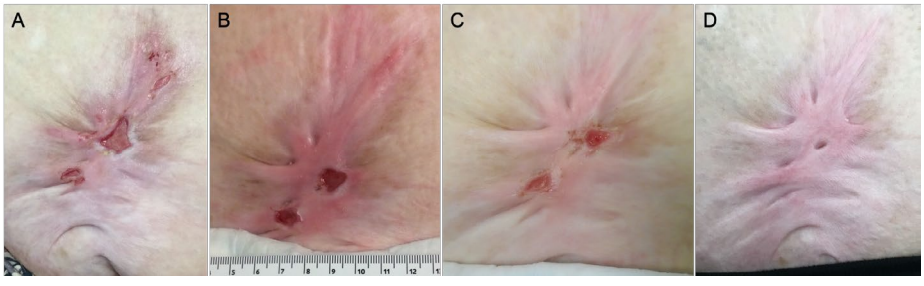
Non-healing ulcers can develop in areas of scarring. Previous reports have demonstrated success treating select chronic ulcers in the presence of scar contractures with AFR, citing decreased tension from improved scar pliability and texture, along with potential wound debridement, biofilm disruption, and molecular changes in the skin.[1,9-13] We present a case of traumatic scarring with non-healing ulceration treated with AFR to facilitate wound healing and then review the literature on this indication for AFR.

CASE REPORT

A 69-year-old obese and hypertensive female presented with a two-year history of multiple chronic, non-healing ulcers on the central abdomen with surrounding scarring refractory to standard wound care. Four years prior, a dermatitis of unspecified etiology developed, and ulceration occurred. The cause of the ulceration was unclear but pruritus and aggressive scratching were thought to have contributed per chart review. Months later, she underwent an Oasis® grafting procedure. The graft became pruritic and the wounds returned, grew in size, and became increasingly painful. Biopsies were performed to rule out malignancy, fungal infection, and vasculitis. The wounds were repeatedly infected and did not respond to wound care, debridement, or hydrotherapy.

After multiple cycles of wound-improvement and recurrence, the wound-care specialist referred the patient for AFR in an effort to assist with wound healing. On physical exam, multiple open erosions on the central abdomen ranging from 1 to 3 cm in size were present with surrounding contracted scar tissue measuring about 8 cm x 5 cm. After evaluation, we proceeded with AFR using a 2940 nm Er:YAG laser (Sciton, Profractional, Palo Alto, CA). Prior to each laser application, the treatment area was topically anesthetized for 1 hour, cleaned

FIGURE 1. The appearance of the patient's scar and non-healing ulcer (A) upon presentation, (B) three weeks after the first laser treatment, (C) immediately prior to the third treatment, and (D) immediately prior to the fourth and final AFR treatment. The patient did not return for follow-up after the fourth treatment.



with chlorhexidine followed by sterile water, then carefully dried. Appropriate eyewear and masks were worn, and a smoke evacuator was used. The patient was treated four times at 6 to 8-week intervals using a fractionated 2940 nm Er:YAG Profractional laser (Sciton, Palo Alto, CA) with settings of 5.5% density and fluence ranging from 162.5-187.5 J/cm^2. The ulcer and surrounding area of scar were treated. The open wounds healed completely over the course of treatment (Figure 1). No adverse effects or complications were observed.

DISCUSSION

Lasers are known to improve scars and are commonly used by dermatologic, plastic and burn surgeons to decrease scar associated morbidity.[14] AFR was first introduced in 2007 and has subsequently become widely accepted as a first-line treatment for traumatic scarring.[7,8] We report a case where AFR was used to mitigate scarring and heal a chronic ulcer refractory to other treatments. Complete healing of the chronic wounds was achieved.

Prior works (Table 1) have evaluated AFR for the healing of chronic wounds.[1,9-12] Cases presented by Uebelhoer et al and Shumaker et al included severe scarring, contractures, and chronic nonhealing wounds from burns[1] and an explosive device blast[9] refractory to split-thickness skin grafting, physical therapy, and proper wound care. The scars on both patients were treated with CO_2 AFR using fluences ranging from 17.5 to 50 mJ and densities between 5 and 15%. The chronic wounds were treated with lower fluences and 3 to 5 weeks after a single AFR treatment, the ulcers in these patients were completely re-epithelialized. Another 3-patient case series by the same group included nonhealing wounds and severe scarring after explosive device injuries and reported complete reepithelization after AFR.

Additional case reports have been published on nonhealing wounds in elderly patients, resulting from trauma and Mohs micrographic surgery, that responded to AFR.[11] Laser parameters included 30 mJ of energy at 5% density applied to the base of the wounds and 50 mJ to the surrounding skin for only one treatment, and complete healing was observed after 3 to 6 weeks, including in one diabetic patient.[11] In another pilot study, ultrapulsed CO_2 laser at 4J was administered weekly to nine patients with diabetic ulcers with exposed bone.[15] After a maximum of six treatments, four patients completely healed, one developed granulation tissue, three did not heal, and one underwent minor amputation.[15] In the same study with the same treatment parameters, AFR was combined with platelet-rich plasma for the treatment of diabetic foot ulcers with exposed bone in five elderly patients, two of which healed in three months, two more developed granulation tissue, and the final patient saw no improvement and underwent amputation.[15]

Reported cases of AFR application in chronic wounds of pediatric patients have also demonstrated benefit.[12] Krakowski et al used AFR on an 8-year-old healthy female with restrictive scarring and a nonhealing wound of eight months duration on her forearm from a chemical burn. Aggressive cryotherapy caused nonhealing wounds in a 17-year-old healthy male, which failed to heal after proper wound care, possibly due to recurrent trauma from football practice. The chronic wounds in both cases were treated twice using ablative fractional CO_2 at a fluence of 50 mJ and density of 5%, resulting in complete re-epitheliazation and improvement in scar texture and pliability.[12]

The method of wound closure prompted by AFR warrants exploration. One theory is that AFR allows local relaxation of tissue and perhaps generation of additional collagen, relaxing tension in the scar area and allowing chronic wounds to close. By improving the pliability of the surrounding skin, oxygen circulation to the wound may also be increased, fostering more rapid healing.[11] Other theories suggest AFR of chronic wounds exerts mechanical effects, stimulates collagen remodeling and triggers angiogenesis to activate a more effective wound healing process.[16]

AFR has shown efficacy in the treatment of acute induced wounds in diabetic mice, more effectively reducing the size of the original wound when compared to natural healing.[17] In this study, treatment groups exhibited significantly increased vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) mRNA expression with reductions in the expression of transformation growth factor-ß (TGF-ß) mRNA.[17]

TABLE 1.

Summary of Prior Cases

Publication	Age	Sex	Injury	Location	Laser	Settings	No. of Tx	Outcomes
Uebelhoer et al 2012[1]	52	M	Burn scar with contracture and non-healing ulcer	R elbow	PDL AF CO_2	4 J/cm^2 fluence, 1.5 ms pulse duration, 10 mm spot size 40 mJ fluence (20 mJ at wound base), 5% density	1	2 weeks post: additional 12 degrees extension. 5 weeks post: increased extension and full re-epitheliazation of the ulcer.
SHUMAKER et al 2012[9]	22	M	Explosive device blast with poor skin mobility with skin fragility and chronic ulcers	L leg amputation stump	AF CO_2	17.5-50 mJ fluence, 5% to 15% density with higher fluences necessitating decreased density	2	3 weeks post initial treatment: significant interval improvement in wound healing skin pliability, and durability allowing prosthetic use. 3 months post final treatment: Progressive improvement and undergoing rehabilitation and walking.
Shumaker et al 2012[10]	26	M	Explosive device blast with poor skin mobility with skin fragility and chronic ulcers	R leg amputation stump	AF CO_2	50 mJ, 5% density, 250 µs pulse duration, 120 µm spot size	2	8 months post final treatment: improvements in texture, pigmentation, and skin pliability. Complete resolution of ulcers.
	28	M	Explosive device blast with hyper-trophic graft site and persistent erosion	R amputation stump	AF CO_2	30 mJ, 5% density, 250 µs pulse duration, 120 µm spot size	2	Complete re-epithelialization of erosion 6 days post treatment. Improved skin texture and pliability.
	39	M	Explosive device blast with persistent ulcer and scar contracture	R elbow	AF CO_2	50 and 30 mJ, 5% density, 250 µs pulse duration, 120 µm spot size	3	Sustained healing of the ulcer during follow-up. Improved skin pliability and range of motion.
Phillips et al 2015[11]	70	F	Degloving injury with non-healing wound	Dorsum of foot	AF CO_2	50 mJ fluence (30 mJ at wound base), 5% density	1	Wound was completely healed 6 weeks after treatment.
	70	M	Non-healing Mohs surgical wound	R shin	AF CO_2	50 mJ fluence (30 mJ at wound base), 5% density	1	Wound was completely healed 3 weeks after treatment.
Krakowski et al 2016[12]	8	F	Scalding chemical burn injury with non-healing wound from repetitive friction	L forearm with contractures	AF CO_2	50 mJ fluence, 5% density	2	2 months post initial treatment: near-complete healing. 2 months post final treatment: complete re-epithelialization with improved skin pliability and texture.
	17	M	Aggressive cryotherapy of verruca vulgaris; non-healing wounds resulting from repeated football practice	L shin	AF CO_2	50 mJ fluence, 5% density	2	1 month post initial treatment: near complete granulation. 1 month post final treatment: complete healing. 4 months post final treatment: complete healing with residual post-inflammatory dyspigmentation.
This report	69	F	Rash subject constant scratching	Abdomen	AF Er:YAG	162.5-187.5 J/cm^2, 5% density	4	The open wound gradually healed over the course of treatment. No adverse effects were observed.

AF: Ablative Fractional; PDL: Pulsed dye laser; Er:YAG: Erbium yttrium aluminum garnet laser; CO_2: Carbon dioxide laser

Discussions of histological and biochemical changes involved in AFR have focused on the upregulation of TGF-ß, heat shock proteins (HSP), and matrix metalloproteinases (MMP).[18] TGF-ß signaling is often documented as suppressed in chronic wounds but its role in wound healing is still unclear.[18-21] HSPs have been established as regulators of the wound healing response by promoting or suppressing TGF-ß expression and fibrosis.[18,22-30] Additionally, different MMPs are stimulated throughout different phases of the wound healing process after AFR, regulating collagen synthesis and degradation.[18,31]

It is important to note that not every non healing ulcer in an area of scarring would be a good candidate for laser treatment. Malignancy and infection need to be ruled out with appropriate techniques, including biopsy and culture. The potential contribution of vascular compromise must also be considered. However, once other contributing factors are explored, then AFR may be considered.

AFR has revolutionized scar treatment and, as demonstrated by this case and review, can benefit select patients with chronic wounds in the setting of scarring. AFR should be considered for non-healing ulcers in areas of scarring, as it can provide the potential for relief for these suffering patients.

CONCLUSION

AFR can be considered for non-healing ulcers in areas of scarring, once malignancy and infection are ruled out. There are multiple theories regarding the mechanism of action, but further investigation is warranted.

DISCLOSURES

The second author is a consultant for Sciton Inc., who provided the device used in this case report.

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AUTHOR CORRESPONDENCE

Kristen M. Kelly MD
E-mail:..... kmkelly@hs.uci.edu

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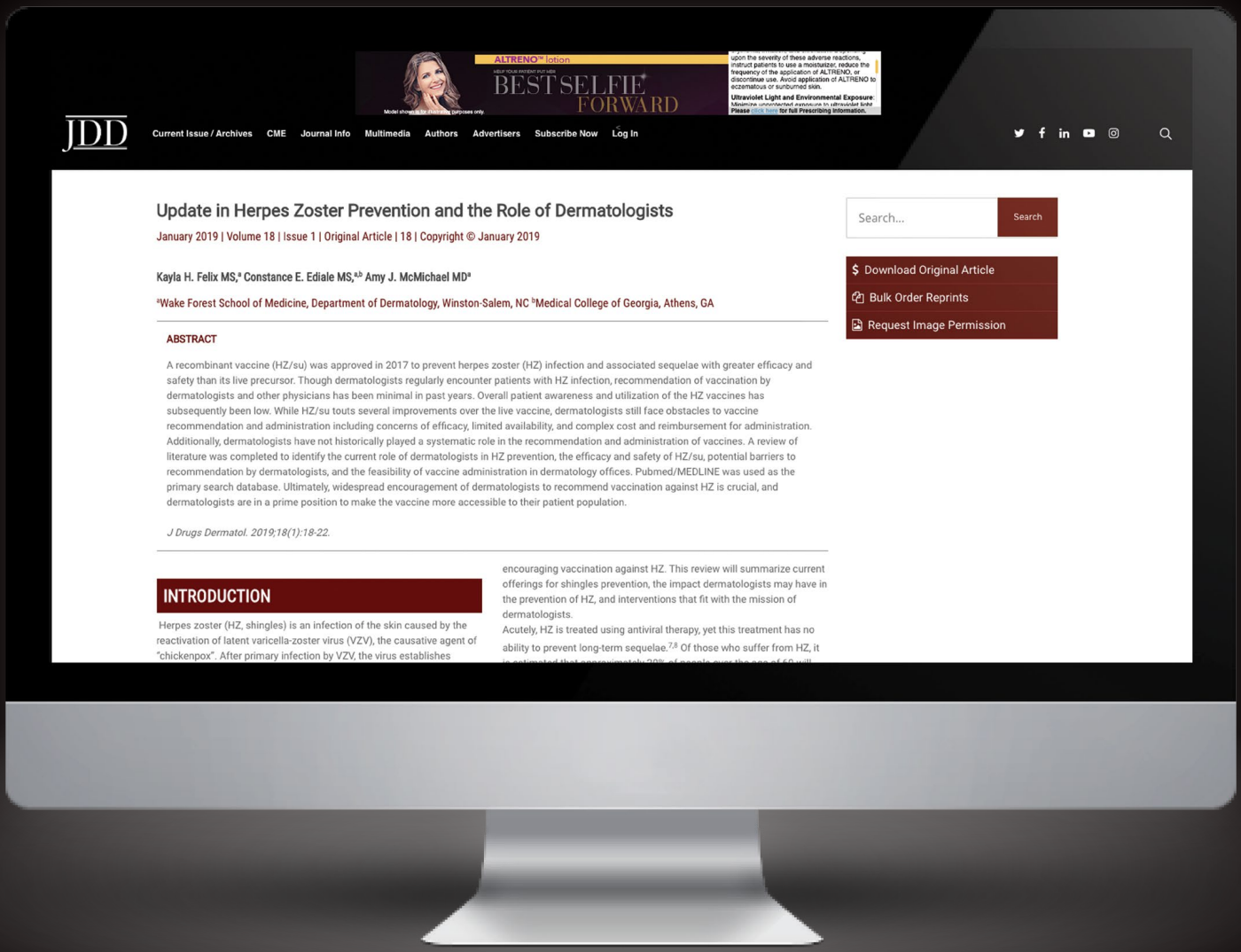

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

The Association of Professors of Dermatology Program Directors Task Force and Residency Program Transparency Work Group Guidelines on Residency Program Transparency

David Rosmarin MD,[a] Adam J. Friedman MD,[b] Nicole M. Burkemper MD,[c] Kristin M. Nord MD,[d,e] Andrea T. Murina MD,[f] Jennifer T. Huang MD,[g,h]

[a]Department of Dermatology, Tufts Medical Center, Boston, MA
[b]Department of Dermatology, George Washington School of Medicine and Health Sciences, Washington, DC
[c]Department of Dermatology, Saint Louis University School of Medicine, St. Louis, MO
[d]Department of Dermatology, Stanford University School of Medicine, Stanford, CA
[e]Dermatology Service, VA Palo Alto Healthcare System, Palo Alto, CA
[f]Department of Dermatology, Tulane University School of Medicine, New Orleans, LA
[g]Department of Dermatology, Harvard Medical School, Boston, MA
[h]Dermatology Program, Boston Children's Hospital, Boston, MA

Socioeconomic and racial disparities continue to plague the house of medicine and importantly the current generation of trainees. One clear area in need of reform is the U.S. dermatology residency application process.[1,2,3] The charge of the Transparency Work Group, a subcommittee of the Association of Professors of Dermatology Program Program Directors Task Force, is to improve the dissemination of relevant program-specific information to applicants. Enhanced program transparency may improve the ability of applicants to make informed choices regarding the selection process and increase trainee and program satisfaction with the match. In light of the recent COVID-19 pandemic which has significantly impacted the opportunity for applicants to experience programs firsthand, the need for more transparent communication between programs and applicants has heightened exponentially.

The Work Group distributed a survey to medical students, residents and program directors to assess perceptions of dermatology residency program transparency.[4] The survey found that the majority of both trainees and program directors feel there is currently inadequate transparency. The main barrier to transparency cited by program directors was lack of guidelines. To address this deficit, the Transparency Work Group has created the following recommendations for residency programs based on the data generated from the aforementioned survey (Table 1):

1. Maintain an up-to-date program website.

First and most importantly, residency programs should keep an up-to-date website as over 90% of trainees utilize this source for program-specific information.[4] In addition to the items listed in Table 1, changes to the selection and recruitment process due to the COVID-19 pandemic should be outlined on each program's website. It is preferable to have an updated website before applications can begin to be submitted.

TABLE 1.

Transparency Work Group Recommendations.

Category	Strongly Recommended	Encouraged
Method of information dissemination	• Up-to-date website	
Selection criteria	• Board score cut-off • Letter of recommendation requirements • Research requirements • Other requirements and exclusion criteria • Special consideration for certain applicant groups	• Emphasis on specific elements of application (e.g. grades, advanced degrees
Interview process	• Interview dates • Number of interview spots and resident positions • Interview format	• Etiquette for communication • Resident involvement in selection
Program priorities	• Current resident/faculty demographics and interests • Mission statement • Diversity initiatives	• Resident life • Psychosocial/wellness support
Program requirements and opportunities	• Rotation/call/didactic schedules • Hospital locations and patient populations • Subspecialty clinics	• Elective and research opportunities • Psychosocial and/or wellness initiatives

2. Disclose any exclusion criteria for application review.
Every program should disclose any exclusion criteria for application review. This includes but is not limited to USMLE scores, doctorate type (allopathic vs osteopathic) or location (US or foreign) of medical school, research or letter of recommendation requirements, and prior residencies.

3. State program-specific interview information.
Advanced planning can help to reduce both the psychosocial toll on applicants during the application process. Programs should clearly state interview dates and format, number of interview spots, resident positions available, and other expectations of the interviewee, including preferred etiquette for communication.

4. Share program-specific priorities.
Programs should share their mission statement, and special considerations for certain applicant groups such as scientific candidates, underrepresented minorities, or local/regional candidates. Diversity initiatives and current resident and faculty demographics and career interests can also help applicants better understand the priorities of the training program.

5. Provide information about program requirements and opportunities.
The Work Group encourages programs to disclose rotation/call/consult/didactic schedules, elective and research opportunities, psychosocial and/or wellness initiatives, and subspecialty clinics.

These guidelines have been designed to improve transparency in dermatology residency selection and are one of many steps that need to be taken to make the application and interview process more accessible and equitable for our future colleagues.

DISCLOSURES

Drs. Burkemper, Friedman, Huang, Murina, Nord, and Rosmarin are members of the Association of Professors of Dermatology Program Directors Task Force and Residency Program Transparency Work Group. Additionally, Dr. Burkemper serves as the dermatology residency program director at Saint Louis University; Dr. Friedman serves as the dermatology residency director at George Washington University, Dr. Huang serves as the dermatology residency program director at Harvard University; Dr. Murina serves as the dermatology residency associate program director at Tulane University; Dr. Nord serves as the dermatology residency program director at Stanford University; Dr. Rosmarin serves as the dermatology residency program director at Tufts Medical Center.

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AUTHOR CORRESPONDENCE

Jennifer T. Huang MD
E-mail:..... Jennifer.Huang@childrens.harvard.edu

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Geographic Variations in Biologic Therapy and Disease Characteristics: A Pilot-Study in the Corrona Psoriasis Registry

Clinton W. Enos MD,[a] Katie A. O'Connell MS,[a] Ryan W. Harrison MS,[b] Robert R. McLean DSc MPH,[b] Blessing Dube MPH,[b] Abby S. Van Voorhees MD[a]

[a]Eastern Virginia Medical School Department of Dermatology, Norfolk, VA

[b]Corrona, LLC, Waltham, MA

The American Academy of Dermatology and the National Psoriasis Foundation recently published extensive guidelines for the management of psoriasis with biologics.[1] However, little is known about geographic variation in the use of these medications. The Corrona Psoriasis Registry is a prospective, multi-center, non-interventional registry for patients with psoriasis under the care of a dermatologist with sites across the United States (Figure 1a). Here, in a pilot analysis of 2018 Corrona data, we investigated geographic variations, based on US Census Divisions, in biologic use by class and patient disease characteristics.

There were 2896 newly enrolled patients on biologic therapy in 2018: 1691 initiated biologic therapy at/after enrollment (initiators) and 1205 had started biologic treatment up to 12-months prior to enrollment (prevalent users). Of the newly enrolled, 24.5% were in the Northeast (NE), 14.4% in East North Central, 11.9% in Mountain-West North Central, 17.8% in South Atlantic, 10.7% in East South Central (ESC), 9.5% in West South Central (WSC), and 11.2% in Pacific (Table 1). Mean age was 50.1 (SD=14.6) and the majority were Caucasian (80.0%), utilized private insurance (73.8%), and had BMI >30 kg/m^2 (52.6%). The most frequently reported comorbid diseases were hypertension (38.2%), hyperlipidemia (27.0%), and diabetes mellitus (16.4%). Mean duration of psoriasis was 14.3 (SD=13.1) years. Moderate disease by Body Surface Area (BSA, 3–10%) was the most commonly reported severity level (41.9%). 44% of patients starting therapy were biologic naïve.

Among geographic divisions, the ESC division had one of the highest frequencies of obesity (58.8%) and the largest frequencies of current smokers (24.5%), hypertension (44.8%), hyperlipidemia (33.2%), and diabetes mellitus (23.9%). The ESC also had the greatest frequency of very severe disease (BSA >20%) (22.6%) and the lowest proportion of biologic naïve patient drug starts (36.1%).

Biologic therapy varied geographically: overall, IL-17 inhibitors (IL-17i) were used the most frequently (44.5%) compared to IL-12/23i and 23i (35%) and TNF inhibitors (TNFi) (20%). The NE was the only region, overall, that utilized the IL-12/23i and 23i class more than the other classes (Figure 1b). When initiating biologic therapy at/after enrollment, TNFi and IL-17i were proportionally chosen more frequently in the ESC (29.1% and 49.8%, respectively) compared to the remaining census divisions; while the IL-12/23i and 23i were more frequent in the NE (48.9%) (Figure 1c). When considering those entering the registry as a prevalent user, the Pacific had the largest proportion on TNFi (35.9%), the ESC on IL-12/23i and 23i (42.5%), and the WSC on IL-17i (55.8%) (Figure 1d).

Limitations to this study are that the Corrona registry is not a random, population-based, representative sample; the registry cohort is comprised of patients invited to participate in the registry by their dermatologists. Regions are derived from the practice location, not patient home addresses. Some regions are underrepresented compared to others, and participating sites may not represent the true overall region.

Despite these caveats, little is known regarding the presence of geographic trends in both the use of biologics for psoriasis and the potential impact on patient outcomes.[2-4] The unadjusted analyses here suggest that in the US there are geographic variations in the use of biologic classes for the treatment of psoriasis. Interestingly, there were also geographic differences in psoriasis severity and prevalence of associated metabolic comorbid diseases. In support of these findings, we previously identified hot-spots of moderate-to-severe and severe psoriasis in the ESC among respondents to the 2016/2017 National Psoriasis Foundation Annual Surveys using geographic information systems.[5] This geographic trend is strengthened with the known relationship between psoriasis severity and metabolic syndrome[6] and the fact that the southern region of the US is burdened with a high prevalence of diabetes and metabolic disease.[7-8] How geographic variations in treatment patterns and disease characteristics ultimately impact patient outcomes will be a topic of future research. The Corrona Psoriasis Registry provides a unique opportunity to investigate these real-world trends.

November 2020 1120 Volume 19 • Issue 11
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Journal of Drugs in Dermatology

FIGURE 1. Geographic variation of biologic class use in the Corrona Psoriasis Registry in 2018. (a) Distribution of Corrona Psoriasis Registry sites across the United States; (b) Frequencies of biologic class use overall; (c–d) Frequencies were also calculated for those initiating therapy at or post-enrollment (initiators), representing an active clinical decision, and for those who initiated therapy within 12 months prior to enrollment (prevalent users), representing an historical clinical decision. All patient initiations (with violation of independence assumption): (b) All initiations (prevalent and initiators at/after enrollment): Drug class vs region, $P<0.001$. (c) Initiators: Drug class vs region, $P<0.001$. (d) Prevalent users: Drug class vs. region, $P<0.001$. Additionally, Chi-square test was also performed for association at patient-level data, all $P<0.001$. TNF inhibitors included: certolizumab pegol, adalimumab, etanercept, and infliximab; IL-17 agents included: secukinumab, ixekizumab, brodalumab; IL-12/23 inhibitor included: ustekinumab; IL-23 inhibitors included: tildrakizumab, and guselkumab. Note that the IL-12/23 and IL-23 classes were combined for all analyses.

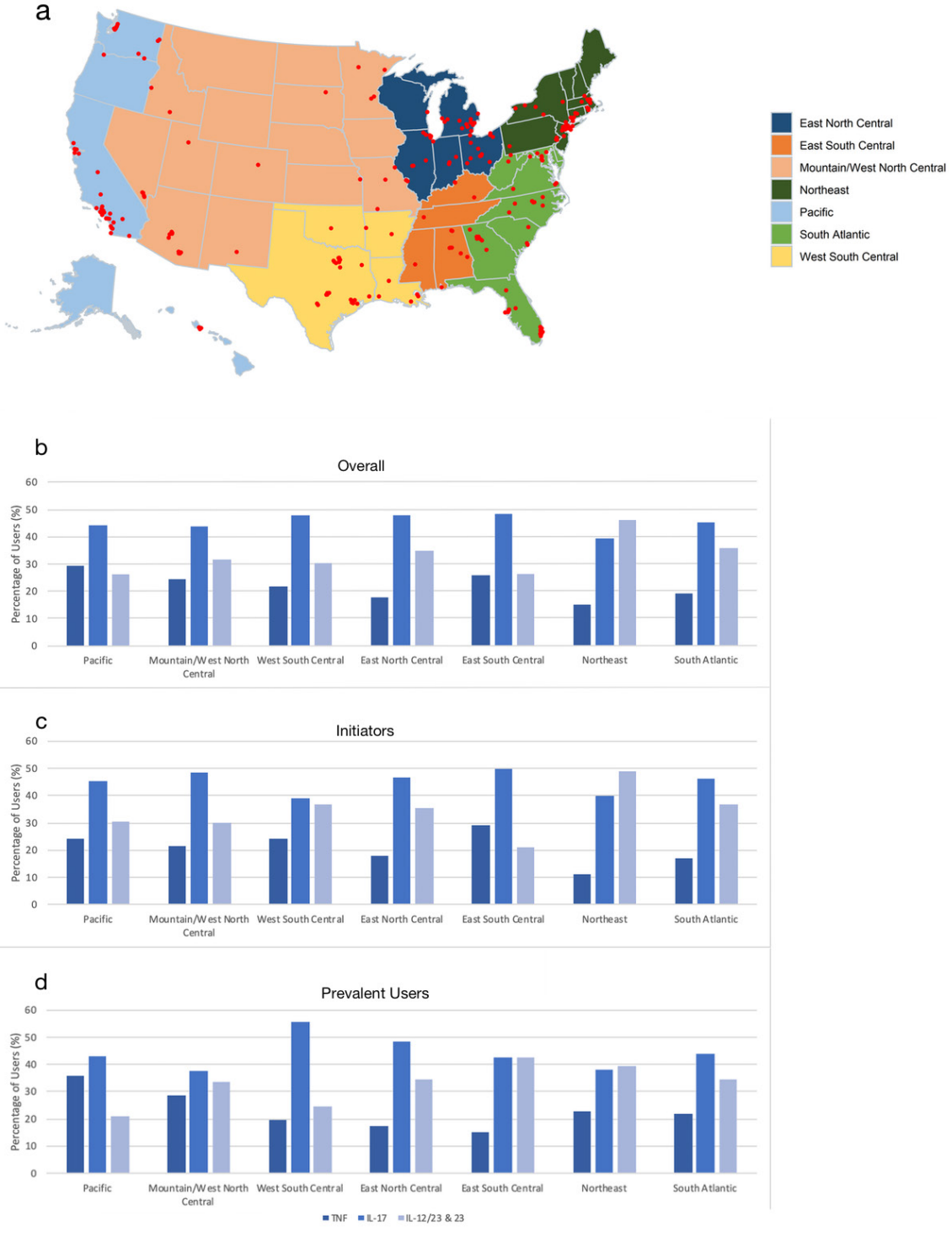

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TABLE 1.

Characteristics of Newly Enrolled Patients in the Corrona Psoriasis Registry on a Biologic Therapy in 2018, by US Census Division

	Pacific	Mountain/ West North Central	West South Central	East North Central	East South Central	Northeast	South Atlantic	*P*-Value	Total
Total (N)	323	346	275	417	310	711	514	--	2896
Age, mean (SD)	49.9 (15.3)	49.9 (13.7)	48.7 (15.1)	49.9 (14.3)	49 (13.5)	50.5 (15.3)	51.0 (14.4)	0.380*	50.1 (14.6)
Female sex, n (%)	124 (38.4)	174 (50.3)	134 (48.7)	196 (47.0)	192 (61.9)	329 (46.3)	260 (50.6)	<0.001**	1409 (48.7)
Race, n (%)	--	--	--	--	--	--	--	<0.001^	--
White	136 (42.1)	289 (83.5)	220 (80.0)	384 (92.1)	296 (95.5)	567 (79.7)	426 (82.9)	--	2318 (80.0)
African American	6 (1.9)	9 (2.6)	18 (6.5)	7 (1.7)	11 (3.5)	45 (6.3)	50 (9.7)	--	146 (5.0)
Asian	116 (35.9)	13 (3.8)	0 (0)	15 (3.6)	0 (0)	52 (7.3)	11 (2.1)	--	217 (7.5)
Other	65 (20.1)	35 (10.1)	28 (10.2)	0 (0)	0 (0)	47 (6.6)	27 (5.3)	--	215 (7.4)
Hispanic, n (%)	50 (15.9)	32 (9.5)	68 (25.6)	0 (0)	0 (0)	62 (8.9)	73 (14.3)	<0.001**	306 (10.8)
Insurance, n (%)									
Private	193 (59.8)	263 (76.0)	219 (79.6)	311 (74.6)	213 (68.7)	531 (74.7)	406 (79.0)	<0.001**	2136 (73.8)
Medicare	63 (19.5)	52 (15.0)	47 (7.1)	77 (18.5)	59 (19.0)	127 (17.9)	85 (16.5)	0.787**	510 (17.6)
Medicaid	88 (27.2)	42 (12.1)	11 (4.0)	49 (11.8)	71 (22.9)	83 (11.7)	35 (6.8)	<0.001**	379 (13.1)
No insurance	9 (2.8)	7 (2.0)	0 (0)	13 (3.1)	0 (0)	6 (0.8)	25 (4.9)	<0.001**	72 (2.5)
Smoking history	--	--	--	--	--	--	--	<0.001^	--
Total (n)	318	341	268	413	310	696	503	--	1199
Never, n (%)	195 (61.3)	158 (46.3)	159 (59.3)	162 (39.2)	142 (45.8)	331 (47.6)	279 (55.5)	--	1426 (50.1)
Former, n (%)	71 (22.3)	109 (32.0)	73 (27.2)	158 (38.3)	92 (29.7)	265 (38.1)	154 (30.6)	--	922 (32.4)
Current, n (%)	52 (16.4)	74 (21.7)	36 (13.4)	93 (22.5)	76 (24.5)	100 (14.4)	70 (13.9)	--	501 (17.6)
Current Alcohol Use, n (%)	--	--	--	--	--	--	--	<0.001^	--
Total (n)	323	346	275	417	310	711	514	--	2896
None/Occasional	209 (64.7)	183 (52.9)	134 (48.7)	223 (53.5)	225 (72.6)	368 (51.8)	321 (62.5)	--	1663 (57.4)
Moderate	60 (18.6)	79 (22.8)	64 (23.3)	104 (24.9)	50 (16.2)	202 (28.4)	112 (21.7)	--	671 (23.2)
Daily	28 (8.7)	44 (12.7)	40 (14.5)	43 (10.3)	15 (4.8)	87 (12.2)	56 (10.9)	--	313 (10.8)
Multiple per day	26 (8.0)	40 (11.6)	37 (13.5)	47 (11.3)	20 (6.4)	54 (7.6)	25 (4.9)		249 (8.6)
BMI	--	--	--	--	--	--	--	<0.001^	--
Total (n)	319	338	270	414	306	703	508	--	1211
<25 (Underweight/ normal), n (%)	88 (26.7)	49 (14.5)	43 (15.9)	55 (13.3)	50 (16.3)	145 (20.6)	97 (19.1)	--	527 (18.4)
25-30 (Overweight), n (%)	107 (33.5)	86 (25.4)	78 (28.9)	120 (29.0)	76 (24.8)	214 (30.4)	147 (28.9)	--	828 (29.0)
>30 (Obese), n (%)	124 (38.9)	203 (60.1)	149 (55.2)	239 (57.7)	180 (58.8)	344 (48.9)	264 (52.0)	--	1503 (52.6)
Duration of Psoriatic Disease in years, mean (SD)	11.9 (11.9)	15.0 (12.8)	11.2 (11.8)	15.4 (13.6)	12.2 (11.6)	16.6 (14.1)	14.1 (13.1)	<0.001*	14.3 (13.1)
Age at Onset of Psoriatic Disease in Years, mean (SD)	38.0 (18.)	34.9 (17.1)	37.5 (16.6)	34.5 (17.3)	36.8 (16.7)	33.9 (17.7)	36.9 (17.2)	0.003*	35.8 (17.4)
BSA- Categorical	--	--	--	--	--	--	--	<0.001^	--
Total (n)	322	346	275	416	310	708	513	--	1221
Mild [0, 3), n (%)	92 (28.6)	131 (37.9)	103 (37.5)	156 (37.5)	102 (32.9)	172 (24.3)	147 (28.7)	--	903 (31.2)
Moderate [3, 10], n (%)	139 (43.2)	144 (41.6)	104 (37.8)	160 (38.5)	117 (37.7)	335 (47.3)	213 (41.5)	--	1212 (41.9)
Severe (10, 20), n (%)	46 (14.3)	29 (8.4)	27 (9.8)	26 (6.2)	21 (6.8)	74 (10.5)	63 (12.3)	--	286 (9.9)
Very severe [20, 100], n (%)	45 (14.0)	42 (12.1)	41 (14.9)	74 (17.8)	70 (22.6)	127 (17.9)	90 (17.5)	--	489 (16.9)

TABLE 1. (CONTINUED)

Characteristics of Newly Enrolled Patients in the Corrona Psoriasis Registry on a Biologic Therapy in 2018, by US Census Division

	Pacific	Mountain/ West North Central	West South Central	East North Central	East South Central	Northeast	South Atlantic	P-Value	Total
Biologic Naïve, n (%)	153 (47.4)	145 (41.9)	134 (48.7)	221 (53.0)	112 (36.1)	288 (40.5)	220 (42.8)	<0.001**	1273 (44.0)
Comorbid Disease									
Total (N)	323	346	275	417	310	711	514	--	2896
Cancer	17 (5.3)	32 (9.2)	21 (7.6)	31 (7.4)	27 (8.7)	60 (8.4)	44 (8.6)	0.626**	232 (8.0)
Cardiovascular disease	22 (6.8)	34 (9.8)	33 (12.0)	37 (8.9)	34 (11.0)	58 (8.2)	48 (9.3)	0.374**	266 (9.2)
Hypertension	117 (36.3)	132 (38.2)	98 (35.8)	163 (39.1)	139 (44.8)	261 (36.7)	196 (38.1)	0.400**	1106 (38.2)
Hyperlipidemia	90 (28.0)	73 (21.1)	62 (22.6)	106 (25.4)	103 (33.2)	200 (28.1)	148 (28.8)	0.024**	782 (27.0)
Diabetes mellitus	52 (16.1)	60 (17.3)	36 (13.1)	66 (15.8)	74 (23.9)	114 (16.0)	73 (14.2)	0.036**	475 (16.4)
Crohn's disease	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.6)	6 (0.8)	5 (1.0)	0.375**	16 (0.6)
Ulcerative Colitis	3 (0.9)	1 (0.3)	2 (0.7)	2 (0.5)	0 (0.0)	6 (0.8)	2 (0.4)	0.697**	16 (0.6)
Indeterminate IBD and other GI disorders	4 (1.3)	9 (2.6)	2 (0.7)	6 (1.4)	5 (1.6)	5 (0.7)	6 (1.2)	0.310**	37 (1.3)

*F-test from ANOVA adjusted for subject random effects. **Chi-square test with Donner adjustment for clustered data. *Chi-square test from patient-level data

DISCLOSURES

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AUTHOR CORRESPONDENCE

Abby S. Van Voorhees MD

E-mail:..... vanvooas@evms.edu

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LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Remission of Refractory PASH Syndrome Using Ixekizumab and Doxycycline

Muhammad I. Gul BS,[a] Vivek Singam BLA,[b] Cody Hanson MD,[c] Brett C. Neill MD,[c] Daniel J. Aires MD JD,[c] Anand N. Rajpara MD,[c]

[a]University of Kansas School of Medicine, Kansas City, KS
[b]University of Missouri-Kansas City School of Medicine, Kansas City, MO
[c]University of Kansas Medical Center, Kansas City, KS

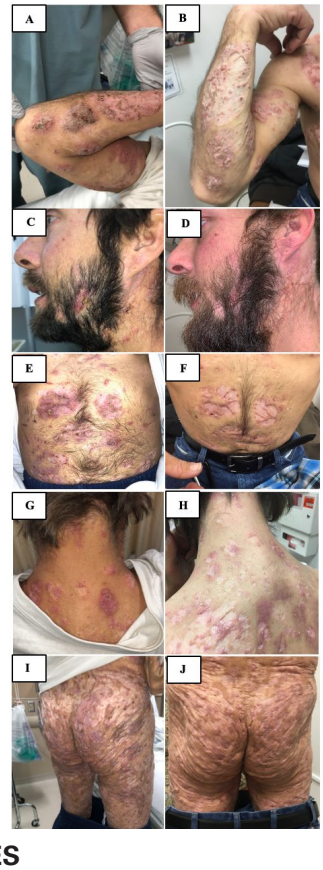
Ixekizumab is a relatively new IL-17 blocking agent recently approved for treatment of psoriasis. We present a first report of successful treatment of PASH syndrome using ixekizumab (Taltz®) and doxycycline in a patient who failed other therapies.

A 37-year-old Caucasian male with a familial history of PASH syndrome presented to the clinic for fatigue, pain and worsening of his cutaneous lesions. At presentation the patient had a 10-year history of vegetative pyoderma gangrenosum (PG), acne fulminans, and Hurley Stage IV hidradenitis suppurativa (HS). His condition was refractory to a 2-month trial of clindamycin and Rifampin PTA therapy, a 4-month trial of adalimumab, and a 5-month trial of ustekinumab. Since Cugno et al recently noted that IL-17 is overexpressed in PASH skin lesions,1 we started the patient on ixekizumab (Taltz®) therapy with a 160 mg loading dose, followed by 80 mg maintenance doses every 2 weeks. Doxycycline 100 mg twice daily was started at the same time. 12 weeks after starting these treatments his PG, acne conglobate and HS remitted (Figure 1). The patient reported significant improvement in quality of life with decreased fatigue and pain.

While PASH has historically have been managed with PTA therapy and surgery, these have shown limited success.1 Biologic agents such as adalimumab, anakinra, and ustekinumab have recently demonstrated safety and efficacy for certain but not all PASH patients.1 Although recent studies have revealed IL-17 plays a critical role in the pathogenesis of PASH,2 to date, there are no reports regarding efficacy of the IL-17-blocker ixekizumab in PASH syndrome.

In December 2017, the FDA approved ixekizumab for treatment of plaque psoriasis and psoriatic arthritis. Compared with other biologic agents such as TNF-blockers, ixekizumab may prove more effective in management of PASH patients due to its IL-17 blocking activity since IL-17 drives several key steps in PASH pathogenesis.[1] These findings may have important implications in future management of PASH patients, especially those who do not respond to PTA therapy, surgical intervention or to other biologic agents.

FIGURE 1. Patient at the time of presentation (left) and after 12-week therapy with ixekizumab (Taltz®) and doxycycline (right).



DISCLOSURES

The authors have no conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Anand Rajpara MD

E-mail:..... arajpara@kumc.edu

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Potential for Teledermatology in Managing and Diagnosing Patients With Cutaneous Lymphomas

Jacob Beer,[a] Edward Hadeler,[b] Keyvan Nouri MD[b]

[a]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[b]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, FL

INTRODUCTION

The COVID-19 pandemic shifted much of the focus of dermatology on the optimal use of telemedicine, particularly in the ambulatory setting.[1] While much of the focus has been on common conditions including psoriasis and atopic dermatitis, it is important to consider its utility for diagnosis and treatment in cutaneous oncology. The United States Cutaneous Lymphoma Consortium recently provided a series of recommendations regarding the treatments for cutaneous lymphomas during the COVID-19 pandemic.[2] They stratify the risk of the patient's lymphoma and compare this risk to the risk of the required treatment in order to provide guidance on which patients should be seen in person and which should be evaluated remotely. Given the immunosuppression in these patients, they advise that telemedicine should be incorporated into care in order to prevent unnecessary exposures.

Teledermatology may provide a crucial role in the management of these patients. Depending on the subtype of cutaneous lymphoma, treatment may consist of topical and/or systemic medications that the patient can use at home.[2] In these cases, the use of virtual platforms for monitoring the patient's progress may provide optimal outcomes. A recent study examining the use of teledermatology to monitor topical therapy in patients with actinic keratoses highlights the potential of this treatment modality.[3] This study notes that patients may require further initial guidance when using virtual platforms in order to ensure compliance and proper use of topical medications.

Establishing the diagnosis of cutaneous lymphomas using digital platforms is presently challenging because of the need for biopsies. Despite this difficulty, digital pathology using whole-slide imaging may provide a role in early detection of cutaneous lymphomas.[4] An early feasibility study examining the use of whole-slide imaging to differentiate between cases of mycosis fungoides and spongiotic dermatitis indicated the strengths of using digital slides for diagnosis.[5] A recent study using a mobile phone camera attached to a microscope adaptor noted a high (93.3%) intraobserver concordance rate for inflammatory and infectious diagnoses made using the adaptor. This presents an opportunity to provide greater access for patients with possible cutaneous lymphomas when combined with existing teledermatology platforms, such as store-and-forward and synchronous methods.

Teledermatology has progressed rapidly over the past several months. While traditional store-and-forward and synchronous platforms may be inadequate for diagnosing cutaneous lymphomas, they may be sufficient for managing many patients with existing diagnoses. Furthermore, when combined with teledermatopathology platforms, including whole-slide imaging, and biopsies obtained by physician extenders, teledermatology is likely to provide an adequate alternative for the diagnosis and treatment of suspected cutaneous lymphoma.

DISCLOSURES

The authors have no conflicts of interest to declare.

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AUTHOR CORRESPONDENCE

Jacob Beer

E-mail:..... Jacob.Beer@pennmedicine.upenn.edu

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Scleroderma in the Setting of Long-term Intermittent Phentermine Use

Jacob Beer BA,[a] Andrea Maderal MD[b]

[a]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[b]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, Miami, FL

Scleroderma is a relatively rare, heterogeneous disease, often involving multiple internal organs that are frequently associated with progressive cutaneous manifestations. The disease occurs predominantly in women, who tend to present at a younger age with more limited disease.[1] We report a case of diffuse cutaneous systemic sclerosis in a patient receiving long-term, intermittent phentermine. The relationship between the patient's use of phentermine and the onset of scleroderma symptoms is considered.

REPORT OF A CASE

A 32-year-old woman presented with new-onset edematous hands and difficulty flexing her fingers. She also noted puffiness of her eyelids and darkening of the skin of her face. She had no significant past medical history. However, she has been prescribed 15 mg/day phentermine on an intermittent basis for several years as an adjunct agent to help her weight loss. She is overweight, but not obese. On review of systems, she complained of reflux symptoms, and endorsed new-onset Raynaud's phenomenon. She denied any shortness of breath.

Physical examination revealed bilateral edematous hands with a waxy appearance, extending just proximal to the metacarpophalangeal joints. She had mildly decreased oral aperture, and faint hyperpigmentation of periorbital skin with mild edema. A biopsy was performed from the right hand, which demonstrated dermal fibrosis consistent with early scleroderma (Figure 1). Antibody testing was borderline positive for an anti-nuclear antibody at a titer of 1:1280, nucleolar pattern. Anti-Scl-70, anti-centromere, and anti-RNA polymerase III antibodies were negative. She was started on amlodipine and mycophenolate mofetil and referred for pulmonary and gastrointestinal evaluation and screening.

FIGURE 1.

DISCUSSION

Phentermine is a sympathomimetic amine, which has been used as an adjunct weight loss agent since its initial approval in 1959. In the 1990s, it was widely used with fenfluroxamine in the combination drug "Fen-Phen". This combination, particularly fenfluroxamine, has been associated with a series of adverse effects, particularly cardiac valvular fibrosis leading to valvular heart disease.[2] While fenfluroxamine was withdrawn from the market after these findings, phentermine was not and since its approval, phentermine has been associated with a series of other adverse reactions including primary pulmonary hypertension, psychosis, and ischemic events.[3]

To date, there has not been a described relationship between phentermine and scleroderma. However, the pathogenesis of scleroderma is not clearly understood, but is thought to occur as a result of abnormalities in vascular, fibrotic and inflammatory pathways. Specifically, systemic sclerosis has been associated with norepinephrine-induced fibrosis.[4] Norepinephrine activates the adrenergic receptor β2, which phosphorylates p38.[4] This induces the production of interleukin 6 (IL-6), which stimulates the production of fibroblasts in collagen, inducing the clinical features of scleroderma.[4] Phentermine has been shown to increase norepinephrine.[3] This norepinephrine release may trigger the onset of fibrosis and a progression to scleroderma. The patient described could be an index case demonstrating a potential link between the two and both of these have fibrosis as a common pathology.

While phentermine has been banned in certain forms, it is still heavily prescribed in the United States as a Schedule IV substance. Phentermine is one of the most widely used anti-obesity drugs, with many patients using it for periods greater than 90 days.[5] Use of this drug is presently limited by the FDA to short-term treatment. As illustrated in the patient presented, phentermine has the potential to easily be prescribed incorrectly. In this case, an overweight patient was prescribed phentermine for long-term use, which may have been a triggering event for her development of scleroderma.

DISCLOSURES

The authors have no conflicts of interest to declare.

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AUTHOR CORRESPONDENCE

Jacob Beer BA

E-mail:..... Jacob.Beer@pennmedicine.upenn.edu

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Revisiting Handwashing – As It Is Absolutely Essential

Graham H. Litchman DO MS,[a] Justin W. Marson MD,[b] Neal Bhatia MD,[c] Brian Berman MD PhD[d]

[a]Department of Dermatology, St. John's Episcopal Hospital, New York, NY

[b]National Society for Cutaneous Medicine, New York, NY

[c]Therapeutics Clinical Research, San Diego, CA

[d]University of Miami Miller School of Medicine, Miami, FL and Center for Cosmetic and Clinical Research, Aventura, FL

ABSTRACT

As the coronavirus pandemic continues into the second half of 2020, states across the US remain steadfast in their search to determine the safest methods of returning to normalcy. Without a readily available, effective COVID-19 vaccine, and as the numbers of infected individuals continues to climb, the best practices to ensure public safety are rooted in good personal hygiene and prevention of transmission of the novel coronavirus SARS-CoV-2. To that end, in addition to properly wearing adequate facial covering, individuals should properly wash their hands to prevent direct auto-inoculation.

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INTRODUCTION

Despite being a technique widely taught from primary school-age, many individuals do not practice adequate hand hygiene and, even pre-pandemic, suffered from economic losses of missed days at work and/or school.[1] Study data have shown that the simple act of handwashing, regardless of other medical interventions, can reduce the transmission of respiratory viruses.[2] Furthermore, handwashing with an adequate antimicrobial product for at least 20 seconds can reduce the risk of transmission of viruses, including respiratory viruses like SARS-CoV-2.[1,3,4] Consistent use of water and soap or alcohol-based sanitizer has been estimated by the World Health Organization (WHO) to reduce pathogen spread up to 50% among healthcare workers.[5] Newer studies are now focusing on "virucidal" properties of alternative and novel agents and combinations.[1]

Sodium hypochlorite (chemically known as NaOCl and more commonly referred to as "Liquid Bleach"), is a chlorine-derived product, that has been used as a disinfectant for over 200 years, and came to prominence in the 1930s. Open wounds were treated with hypochlorite solutions during World War I, which lead to more routine use within hospitals.[6] This paired with aggressive marketing, ultimately lead to "Clorox" becoming the household name for a disinfectant.

The antimicrobial effects of these chlorine-derived products comes from their ability to disrupt the membranes of bacteria, fungi, and viruses as well as induce oxidative damage to the necessary proteins and enzymes for microbial survival.[7] The strengths of chlorine-derived agents are determined by their concentration and the solvent (typically water) in which they are mixed. When NaOCl is added to water the reaction yields hypochlorous acid ion (HOCl) and sodium hydroxide (NaOH) (Figure 1).[5] Because NaOCl is more stable, it usually predominates at equilibrium. However, in more acidic solvents, the concentration of HOCl increases. This increases the potency of the solution's antimicrobial properties given that HOCl is 80–120 times more efficient at eliminating bacteria, viruses, and fungi than sodium hypochlorite.[8,9] Hypochlorous acid on its own is far too caustic and is not appropriate for application to the skin or human body; consequently, it is reserved for disinfecting inanimate objects, demonstrating that its strength comes at a price.[5]

While HOCl may be too caustic in direct applications, modulation of the concentration of the solvent and pH to a more basic 6% sodium hypochlorite dissolved in over 120 liters of water (or a bleach bath) is a corner stone of controlling bacteria levels in patients with atopic dermatitis.[10] Although data on twice weekly bleach baths shows mixed results, newer, less concentrated formulations of NaOCl-based products, including a daily body wash,[11] not only decrease bacterial loads, but are also well-tolerated on skin and far easier to use on a regular basis. Additional studies demonstrated that NaOCl was efficacious in a concentration-dependent manner where a 0.25% solution removed 99.97% of detectable viral particles from the hands[3] after contact time of 15–30 seconds, within the handwashing-timeframe recommended by the CDC.[3,12,13] Furthermore, a recent study has demonstrated reduced detection of Coronavirus by ≥3.50 log10 (≥99.97%) following a 15-second exposure to a 0.006% sodium hypochlorite wash.[13]

FIGURE 1. Chemical reaction between sodium hypochlorite and water. The reaction generally favors the more stable sodium hypochlorite. In more acidic conditions the reaction shifts the equilibrium to the right, producing slightly more of the more potent hypochlorous acid

$$NaOCl + H_2O \rightleftharpoons HOCl + NaOH$$

Various other products have also been examined, some of which utilize active ingredients such as quaternary ammonia salts and phenolic compounds, and are effective after 1 to 10 minutes of contact, depending on preparation (Table 1).[5] While potent, these agents are relegated to surface decontamination of inanimate objects as they can instigate an inflammatory reaction in the mucous membranes as well as the skin.[14] At this time, the more common agents used for handwashing are alcohol-derived products and classic soap and water. Alcohol-based disinfectants with a concentration between 50–90% function by disrupting requisite microbial cell membrane proteins and are highly efficacious in eliminating unwanted microbes.[5] However, overexposure to alcohol-based disinfectants from repetitive applications can deplete the skin of necessary fatty acids, disrupting normal barrier function leading to irritant contact dermatitis.[5] Soap and water are highly effective in decreasing microbial load, however their virucidal properties are highly dependent on the chemical composition of their fatty-acid components.[5] While soap and water do not have the same risk profile for irritant contact dermatitis (unless used in excess) their usage is typically limited by access to running water.[2,5]

TABLE 1.

Common components of virucidal sanitizing agents ranked by increasing reported contact time (ie, time needed for application to maximize antimicrobial activity) of the primary active compound. Note how in combination with additional agents/solvents, the contact time can be dramatically lowered and also change the safety/tolerability profile for use on skin.

Sanitizing Agent	For Surfaces	For Skin*	Contact Time** (mins)[5]	Limitations for Topical Use[15]
Ethanol (EtOH)	+	+	0.5	Irritant contact dermatitis, mucocutaneous irritation, flammable
WHO-I (EtOH 85% v/v, Glycerol 0.725% v/v, Hydrogen Peroxide 0.125% v/v)		+		
WHO-II (Isopropanol 75% w/w, Glycerol 0.725% v/v, Hydrogen Peroxide 0.125% v/v)		+		
Hypochlorous Acid	+		0.5	Mucocutaneous irritation, blistering/burns
Silver Ion, Citric Acid	+		1	Mucocutaneous irritation
Peroxyacetic Acid	+		1	Mucocutaneous irritation, blistering/burns, flammable
Hydrogen Peroxide	+	+	5	Mucocutaneous irritation, skin discoloration, swelling
+ Peroxyacetic Acid	+		1	
+ Ammonium Carbonate, Ammonium Bicarbonate	+		5	
Sodium Hypochlorite	+		10	Redness, pain
6% v/v + Sodium Carbonate	+		0.5	Redness, pain
0.25% g/g		+	0.5	
0.006% solution		+	0.25-0.5	
Quaternary Ammonium	+		10	Mucocutaneous inflammation, possible allergenic potential
+ Ethanol	+		1	
+ Isopropanol	+		0.5	
Phenolic Acid	+		10	Potential mutagen, mucous membrane irritation, reproductive toxicity
Sodium Chlorite	+		10	Redness, pain

*Composition/concentration dependent
**Contact times based for surface disinfectant use

Effective handwashing is capable of not only reducing the pathogenic load on an individual's hands but also preventing illness, thereby theoretically reducing significant economic fallout. The key to harnessing this tool lies in not only practicing proper technique for the recommended 20 seconds, but also utilizing appropriate agents to sufficiently decrease the viral load that individuals may unwittingly carry. Age-old therapeutics are being researched, refashioned, and recombined into newer fungicidal, bactericidal, and virucidal agents for use in our surroundings and on our persons. Pandemic or not, handwashing has proven time and time again to be a public health cornerstone for maintaining the well-being of oneself and of the community.

CONCLUSIONS

A key habit to reduce risk of infection while maintaining healthy skin must include proper disinfection with safe, gentle, and effective topical cleaning products that are not only quick and accessible, but also are safe and carry few, if any, adverse effects.

DISCLOSURES

Dr. Berman is a member of the scientific advisory board – TopMD. The other authors have no relevant conflicts to declare.

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AUTHOR CORRESPONDENCE

Brian Berman MD PhD
E-mail:..... bbmdphd@gmail.com

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1)

A 50-year-old woman presents to clinic for evaluation of multiple facial papules. She states she first started noticing the lesions develop in her 30s. She also has growths on her scalp. She has several family members with similar bumps on their face. Biopsy of one of her facial lesions show well-circumscribed nests of basaloid cells in the dermis. You decide to refer the patient for genetic testing. Which of the following genes do you expect to be affected?

A. CYLD
B. FLCN
C. PTCH
D. PTEN
E TSC1

2)

Patient is an 84-year-old woman who presents with new pruritic urticarial plaques on her legs, thighs, and upper back. They have been expanding for 2 weeks and are recalcitrant to topical steroids. A biopsy was performed, which showed spongiosis and abundant eosinophils in the dermis. DIF shows linear deposition of C3 and IgG along the dermal-epidermal junction. Which of the following conditions have the same antigenic target as in the disease seen in this patient?

A. Herpes gestationis
B. Epidermolysis bullosa acquisita
C. Bullous lupus erythematosus
D. Ocular-predominant mucous membrane pemphigoid
E IgA pemphigus

3)

A 6-year-old male patient presents for what his parents believe are multiple bug bites on the trunk and extremities. They note that they have not faded after 6 weeks and will sometimes become red and itchy. Physical exam findings are shown below (Figure 1). Which medication is should be avoided if possible, by this patient?

A. Codeine
B. Penicillin
C. Acetaminophen
D. Cimetidine
E Lidocaine

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The content of these case studies, ideal to review during peer study groups, was developed by Angela Hou, MD and Aaron Fong, MD under the guidance of dermatologist Adam Friedman, MD, Professor and Interim Chair of Dermatology, Residency Program Director, Director of Translational Research, Director of Supportive Oncodermatology Clinic.

Angela Hou, MD
GW School of Medicine
and Health Sciences,
Department of Dermatology

Aaron Fong, MD
GW School of Medicine
and Health Sciences,
Department of Dermatology

Answers

1) The correct answer is A: CYLD

Explanation/Literature Review

This patient likely has Brooke-Spiegler syndrome, and the biopsy is consistent with a spiradenoma. Brooke-Spiegler syndrome is a rare genodermatosis that is characterized by three different adnexal tumors: cylindromas, spiradenomas, and trichoepitheliomas. Cylindromas typically present as dermal papulonodules of the scalp. Spiradenomas can be tender and are usually found on the head and neck. Trichoepitheliomas present as skin colored to pink papules on the face. Brooke-Spiegler syndrome is an autosomal dominant disorder caused by a mutation in the CYLD tumor suppressor gene located on the 16q chromosome. Most lesions are benign and require no further treatment, though patients may seek therapy for tumors that are disfiguring, disabling, or potentially impairing vital functions such as vision or hearing.

FLCN is the gene defect found in Birt-Hogg-Dubé syndrome. Cutaneous findings in Birt-Hogg-Dubé syndrome include fibrofolliculomas, trichodiscomas, and acrochordons. Systemic findings to look for are renal cell carcinoma and spontaneous recurrent pneumothorax. *PTCH* is mutated in Gorlin syndrome, also known as basal cell nevus syndromes. Characteristic findings include multiple early onset basal cell carcinomas, palmoplantar pits, odontogenic keratocysts of the jaw, calcification of the falx cerebri, and medulloblastoma. *PTEN* mutations lead a spectrum of diseases called the PTEN hamartoma tumor syndrome. This group of syndromes include Cowden disease, Bannayan-Riley-Ruvalcaba syndrome, SOLAMEN syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus), and Lhermitte-Duclos disease. Finally, TSC1 mutation is found in tuberous sclerosis. Cutaneous findings in tuberous sclerosis include facial angiofibromas, ash-leaf macules, Shagreen patch, periungual fibromas, and café-au-lait macules.

2) The correct answer is A: Herpes gestationis

Explanation/Literature Review

The patient in this question stem has bullous pemphigoid. Patients with bullous pemphigoid often present with initially urticarial or eczematous plaques, then develop tense bullae. Biopsy shows subepidermal bulla with eosinophilic infiltrate, and the characteristic DIF finding includes linear IgG and C3 along the basement membrane. The antigenic targets for bullous pemphigoid are BP180 (BPAg2) and BP230 (BPAg1).

Herpes gestationis, also known as pemphigoid gestationis, has autoantibodies against BP180 like bullous pemphigoid. This is a rare vesiculobullous eruption that occurs in patients in the second or third trimester of pregnancy. Like bullous pemphigoid it initially starts as extremely pruritic urticarial papules and plaques that progress into tense blisters. The lesions are commonly distributed around the umbilicus. It is important to educate patients that this commonly recurs during future pregnancies, and that the severity often increases with subsequent pregnancies.

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Epidermolysis bullosa acquisita is an acquired autoimmune blistering disease with antibodies targeting collagen type VII. Bullous lupus erythematosus also has antibodies directed at collagen type VII, but tends to improve rapidly to treatment with dapsone, whereas epidermolysis bullosa acquisita is usually recalcitrant to treatment. While mucous membrane pemphigoid can have autoantibodies targeting BP180, in the ocular-predominant subtype targets β4 integrin specifically. IgA pemphigus presents in middle-aged to eldery patients with flaccid vesicles and pustules in an annular or circinate pattern. It has two subtypes: subcorneal pustular dermatosis, in which the target antigen is desmocollin 1, and intraepidermal neutrophilic type, with target antigens desmoglein 1 and 3.

3) The correct answer is A: Codeine

Explanation/Literature Review

This child has maculopapular cutaneous mastocytosis, or urticaria pigmentosa, which is caused by an abnormal accumulation of mast cells in the skin. It is thought to be caused by an activating mutation of the c-KIT gene, which causes enhanced survival and growth of clonal mast cells. Patients typically present with orange-brown macules to papules on the trunk and extremities. They exhibit a characteristic positive Darier sign, where a lesion becomes urticarial or red and itchy upon rubbing due to activation of mast cells. Patients with suspected mastocytosis can be diagnosed clinically, or if uncertain, a lesional skin biopsy can help confirm the diagnosis. Patients should also have a complete blood count, liver function test, and total tryptase level performed to ensure there is no systemic involvement. Furthermore, patient should try to avoid medications that can be known to cause mast cell degranulation. These medications include opioids, such as morphine or codeine, vancomycin, polymyxin B, various medications used in anesthesia such as neuromuscular blockers, and particularly ester anesthetics (amide anesthetics appear to be typically tolerated). Furthermore, in pediatric patients the risk of anaphylaxis is low and some patients are treated with antimediator therapy prior to anesthesia.

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13. Publication Title: Journal of Drugs in Dermatology

14. Issue Date for Circulation Data Below: September 2020

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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Shelley N. Tanner — Shelley N. Tanner, Publisher	09/08/20

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