ISSN: 1545 9616 November 2021 • Volume 20 • Issue 11

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

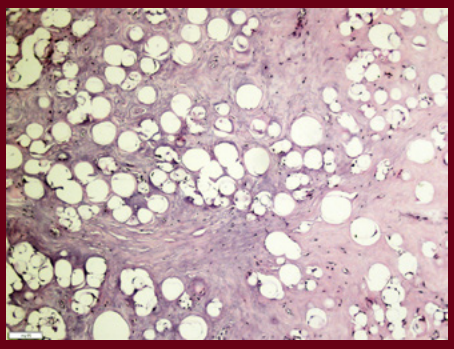


Image credit page 1164

SPECIAL FOCUS: LASERS, LIGHT SOURCES, AND DEVICES

Deoxycholic Acid (ATX-101) for Fat Reduction

Therapeutic Approaches for Treating Molluscum Contagiosum

Skincare for Neonates and Infants: An Algorithm

OTC Products as Adjunctive Acne Care

An Overview of Biologics for Psoriasis

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

ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

For adults with plaque psoriasis

workingtogether

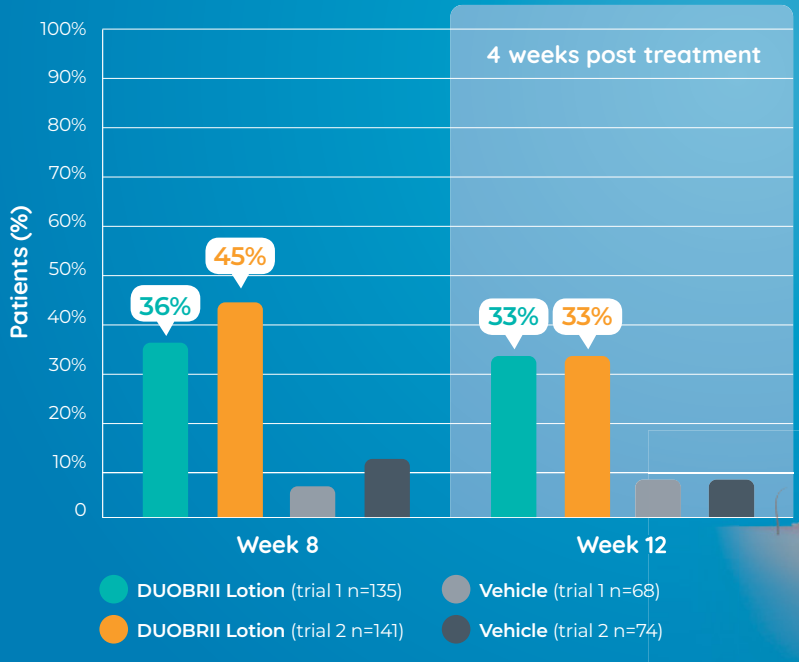
DUOBRII® (halobetasol propionate and tazarotene) Lotion 0.01% / 0.045%

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 dosing; 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 April 12, 2021. **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**

Ortho Dermatologics

®/™ are trademarks of Ortho Dermatologics' affiliated entities. © 2021 Ortho Dermatologics' affiliated entities. DUO.0056.USA.21

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 in full Prescribing Information]*. 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%), excoriation (2%), rash (1%), skin abrasion (1%), and skin exfoliation (1%).

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, and Clinical Pharmacology in full Prescribing Information]*.

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).

Distributed by:
Bausch Health US, LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Bausch Health Companies Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847; 8,809,307; 10,251,895 and 10,478,502

DUOBRII is a trademark of Bausch Health Companies Inc. or its affiliates.

© 2021 Bausch Health Companies Inc. or its affiliates. DUO.0049.USA.21

Based on 9645602 **Revised:** 01/2020 **Issued:** 03/2021

Copyright © 2021

EDITORIAL BOARD

Journal of Drugs in Dermatology

EDITOR-IN-CHIEF
Perry Robins MD

CO-EDITOR-IN-CHIEF
Deborah S. Sarnoff MD

SENIOR EDITORS
Macrene Alexiades MD PhD
Robert Baran MD
Joseph B. Bikowski MD
Dee Anna Glaser MD
C. William Hanke MD
William Levis MD
Ronald L. Moy MD
Keyvan Nouri MD
Neil S. Sadick MD
Gerhard Sattler MD
James M. Spencer MD
Susan H. Weinkle MD

SENIOR ASSOCIATE EDITORS
Kenneth Beer MD
Martin Braun MD
Jeffrey Phillip Callen MD
Jean Carruthers MD
James Q. Del Rosso DO
Lawrence F. Eichenfield MD
Patricia Farris MD
Norman Goldstein MD
Aditya K. Gupta MD PhD
Elizabeth Hale MD
Sherry H. Hsiung MD
Leon H. Kircik MD
Mark Lebwohl MD
Henry W. Lim MD
Flor Mayoral MD
Maurizio Podda MD PhD
Jeffrey Orringer MD
Maritza Perez MD
Kevin Pinski MD
Luigi Rusciani Scorza MD
Ritu Saini MD
Jerome I. Shupack MD
Amy Taub MD
Danny Vleggaar MD
Brian Zelickson MD
Shawn Allen MD
Rex A. Amonette MD
Robert Anolik MD
Martha P. Arroyo MD
Robin Ashinoff MD
Marc R. Avram MD
David E. Bank MD
Jay G. Barnett MD
Eliot F. Battle Jr. MD
Richard G. Bennett MD
Diane S. Berson MD
Ronald R. Branaccio MD
Rana Anadolu Brasie MD
Jeremy A. Brauer MD
Gary Brauner MD
Neil Brody MD PhD
Lance H. Brown MD
Isaac Brownell MD PhD
Cheryl Burgess MD
Karen E. Burke MD PhD
Mariano Busso MD
Valerie Callender MD
Francisco M. Camacho-Martinez MD
Marian Cantisano-Zilkha MD
Alastair Carruthers MD
Roger I. Ceilley MD
Clay J. Cockerell MD
David E. Cohen MD
Julian S. Conejo-Mir MD
Elizabeth Alvarez Connelly MD
Ira Davis MD
Calvin Day MD
Doris Day MD
Jeffrey S. Dover MD
Zoe Diana Draelos MD
Madeleine D. Duvic MD
Mohamed L. Elsaie MD
Joseph C. English III MD
Neil Alan Fenske MD
Rebecca Fitzgerald MD
Alina A. Fratila MD
Alejandro Camps Fresnada MD
Ellen C. Gendler MD
Dore Gilbert MD
David J. Goldberg MD
Leonard H. Goldberg MD
Robert H. Gotkin MD
Gloria F. Graham MD
Pearl E. Grimes MD
John Hawk MD
Michael P. Heffernan MD
William L. Heimer II MD
N. Patrick Hennessey MD
Alysa R. Herman MD
George J. Hruza MD
Shasa Hu MD
Kimberly Huerth MD
Mark J. Jaffe MD
Jared Jagdeo MD
S. Brian Jiang MD
Bruce E. Katz MD
Mark D. Kaufmann MD
Amor Khachemoune MD
Poong Myung Kim MD
Christine Ko MD
David Kriegel MD
Pearon G. Lang MD
Aimee Leonard MD
Mary P. Lupo MD
Alan Matarasso MD
Alan Menter MD
Warwick L. Morison MD
Jenny Murase MD
Rhoda S. Narins MD
Mark Naylor MD
Kishwer S. Nehal MD
Martino Neumann MD
Nelson Lee Novick MD
Jorge J. Ocampo Candiani MD
Philip Orbuch MD
Ariel Ostad MD
Cleire Paniago-Pereira MD
Anna C. Pavlick MD
Christopher R. Payne MD
António Picoto MD
Sheldon V. Pollack MD
Babar K. Rao MD
Wendy E. Roberts MD
Amy E. Rose MD
Steven Rosenberg MD
Lidia Rudnicka MD
Bijan Safai MD
Eli R. Saleeby MD
Fitzgeraldo A. Sanchez-Negron MD
Miguel Sanchez-Viera MD
Julie Schaffer MD
Bryan C. Schultz MD
Daniel Mark Siegel MD
Arthur J. Sober MD
Nicholas A. Soter MD
Jennifer Stein MD
Fernando Stengel MD
Hema Sundaram MD
Susan C. Taylor MD
Emily Tierney MD
George-Sorin Tiplica MD PhD
Ella L. Toombs MD
Irene J. Vergilis-Kalner MD
Steven Wang MD
Ken Washenik MD PhD
Jeffrey Weinberg MD
Robert A. Weiss MD
W. Phillip Werschler MD
Ronald G. Wheeland MD
Jai Il Youn MD
John Zic MD
John A. Zitelli MD

FEATURE EDITORS
Kendra G. Bergstrom MD
Joel L. Cohen MD
Adam Friedman MD
James L. Griffith MD
Marissa Heller MD
Isaac Zilinsky MD

ASSOCIATE EDITORS
Dale M. Abadir MD
William Abramovits MD
Andrew F. Alexis MD MPH

PAST CO-EDITORS-IN-CHIEF
Elizabeth Hale MD (2004)
Susan H. Weinkle MD (2005-2008)
Keyvan Nouri MD (2005-2008)
Sherry H. Hsiung MD (2008)
James M. Spencer MD (2009-2013)

Impact Factor
Impact Factor Score: 2.114*
Normalized Eigenfactor® Score: 0.90773*
Article Influence Score: 0.456*
*Clarivate Analytics, Formerly the IP & Science Business of Thomson Reuters, June 2020

November 2021 Volume 20 • Issue 11

Copyright © 2021

TABLE OF CONTENTS

Journal of Drugs in Dermatology

JDD
DRUGS • DEVICES • METHODS

JOURNAL OF DRUGS IN DERMATOLOGY

ORIGINAL ARTICLES

1150 **Optimizing Outcomes With the 1550/1927 nm Dual Wavelength Non-Ablative Fractional Laser: Experienced User Recommendations**
Paul M. Friedman MD, Anne Chapas MD, Suzanne L. Kilmer MD, Zakia Rahman MD, Wendy Roberts MD, E. Victor Ross MD, Jill S. Waibel MD, Jeffrey S. Dover MD FRCPC

1161 **Laser in the Treatment of Granulomas on the Nose Produced by Polymethylmethacrylate: A Case Series**
Alberto Goldman MD, Uwe Wollina MD, Denise Cantrelli Machado PhD, Daniel Rodrigo Marionwic PhD

1169 **Deoxycholic Acid (ATX-101) for Fat Reduction**
Jyoti Gupta MD, Martin Kassir MD, George Kroumpouzos MD, Andreas Katsambas MD, Hassan Galadari MD, Torello Lotti MD, Uwe Wollina MD, Stephan Grabbe MD, Mohamad Goldust MD

1174 **Single-Center, Prospective, Double-Blind, Evaluator-Blind, non-Randomized, Vehicle-Controlled Trial With a 1927 nm Non-Ablative Fractionated Laser and Topical 0.05% Tretinoin Lotion for Facial Dyspigmentation and Photodamage**
Rawaa Almukhtar MD MPH, Emily Carr MD, Kunal Angra MD, Michael Lipp DO, Monica Boen MD, Mitchel P. Goldman MD

1185 **Therapeutic Approaches and Special Considerations for Treating Molluscum Contagiosum**
Lawrence F. Eichenfield MD, Adelaide A. Hebert MD, Anthony J. Mancini MD, Theodore Rosen MD, Jonathan Weiss MD

November 2021 Volume 20 • Issue 11
Copyright © 2021

Journal of Drugs in Dermatology

ORIGINAL ARTICLES (CONT'D)

1191 **An Open-Label Pilot Study to Investigate Safety and Efficacy of Fixed Combination Tazarotene 0.045% and Halobetasol Propionate 0.01% Lotion for the Treatment of Scalp Psoriasis**
Elif Ozyurekoglu and Leon H. Kircik MD

1195 **The Importance of Skincare for Neonates and Infants: An Algorithm**
Lawrence A. Schachner MD FAAD FAAP, Anneke Andriessen PhD, Latanya Benjamin MD FAAP FAAD, Alanna F. Bree MD, Peter A. Lechman MD MBA FAAP, Ayleen A. Pinera-Llano MD, Leon H. Kircik MD FAAD, Adelaide Hebert MD FAAD

1213 **Recommendations for Using Over-the-Counter Products as Adjunctive Acne Care in Asian Phototypes: Improving Treatment Outcomes and Managing Side Effects**
Anneke Andriessen PhD, Xian Jiang MD PhD, Kanokvalai Kulthanan MD, Chih-Hung Lee MD PhD, Rodney Sinclair MBBS MD FACD, Cheng-Feng Zhang MD PhDf

1222 **Patient-Reported Disease Burden and Unmet Therapeutic Needs in Atopic Dermatitis**
Elizabeth D. Bacci PhD, Anne M. Rentz MSPH, Julia Correll MPH, Evangeline J. Pierce PhD, Amy M. DeLozier MPH, Maria Jose Rueda MD, Wendy Smith Begolka MBS, Lisa Butler MBA

1231 **Effectiveness and Safety of Calcium Hydroxylapatite With Lidocaine for Improving Jawline Contour**
Amir Moradi MD, Jeremy B. Green MD, Joel L. Cohen MD, John H. Joseph MD, Rada Dakovic PhD, Gemma Odena PhD, Amit Verma PhD, Richard Scher MD

1239 **Aminolevulinic Acid 20% Solution Combined With Photodynamic Therapy for Treatment of Actinic Keratoses: A Review**
Joe Gorelick MSN FNP-C,Scott Freeman MCMS PA-CB

BRIEF COMMUNICATIONS

1246 **An Overview of Biologics for Psoriasis**
Rachna Dave MD, Amena Alkeswani MD

1248 **Examining Trends in Dermatology Publications: A 10-Year Follow-up**
Reem Qabas Al Shabeeb MD, Kamaria Nelson MD, Kelley Pagliai Redbord MD

At Dermavant, our mission is to make healthier skin a reality for millions of patients around the world living with chronic skin conditions. That's why we're hard at work, developing novel treatments that deliver groundbreaking science exactly where patients need it—their skin.

Because skin is more than superficial, it's where we live every moment of every day.

Skin deserves more.

dermavant®

SKIN IS A WHOLE LOT MORE THAN SUPERFICIAL

November 2021 Volume 20 • Issue 11

Copyright © 2021 TABLE OF CONTENTS Journal of Drugs in Dermatology

LETTERS TO THE EDITOR

1252 **Patients Frequently Overestimate Their Comprehension of Common Mohs Micrographic Surgery Terms: A Cross-Sectional Survey**
Peter Chow MD, Brett C. Neill MD, Edward W. Seger MD MS, Spyros M. Siscos MD, Jace J. Rickstrew MD, Ian Graham BS, Anand Rajpara MD, Thomas L.H. Hocker MD

1255 **Successful Treatment of Palmoplantar Pustulosis With Apremilast**
Noelle Dorgham MS-III, David Crasto DO, Stanley Skopit DO

1257 **OnabotulinumtoxinA for Systemic Sclerosis-associated Raynaud's Phenomenon: A Multi-Institutional Study on Accessibility and Effectiveness**
Bina Kassamali BA, Sheena Desai BS, Michelle S. Min MD MS, Daniel R. Mazori MD, Camila Villa-Ruiz MPH, Kylee JB Kus, BS Gabriela A. Cobos MD, Joseph Merola MD MMSc, Avery LaChance MD MPH, Ruth Ann Vleugels MD MPH MBA

OFFICIAL PARTNER OF

International Society for Dermatologic Surgery

SKIN OF COLOR UPDATE

ODAC

Publishers
Shelley N. Tanner
Lawrence E. Robins

Executive Editor
Karin Beehler

Associate Editor
Kathleen Leary RN

Associate Publisher
Nick Gillespie

Director, Scientific Communications
Luz Figueroa

Design
Karen Rebbe

Journal of Drugs in Dermatology (JDD) (ISSN 1545-9616) is published monthly for $300 per year US Individual subscriptions/ $350 per year International Individual subscriptions/(Corporate and Institutional rates contact Sales for a quote) by the *Journal of Drugs in Dermatology*, 115 E. 23rd Street, 3rd Floor, Unit 322, New York, NY 10010. Periodicals postage paid at New York, NY and additional mailing offices.

ADVERTISING & CORPORATE & INSTITUTIONAL SALES: Contact Nick Gillespie at 646-453-5711
e-mail: nick.gillespie@jddonline.com

REPRINTS & PERMISSIONS: Contact Luz Figueroa at 646-736-4338
e-mail: luz.figueroa@jddonline.com

SUBSCRIPTIONS: Email info@jddonline.com or call 212-213-5434 ext. 2

POSTMASTER: Send address changes to the Journal of Drugs in Dermatology,
115 E. 23rd Street, 3rd Floor, Unit 322, New York, NY 10010.

Journal of Drugs in Dermatology (JDD)
is indexed in MEDLINE®/PubMed® and is published monthly by the
Journal of Drugs in Dermatology
115 E. 23rd Street, 3rd Floor, Unit 322, New York, NY 10010
telephone: 212-213-5434 | fax: 212-213-5435 | JDDonline.com

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in electrical or other forms or by any means without prior written permission from the *Journal of Drugs in Dermatology* (JDD). This publication has been registered with the Library of Congress (ISSN: 1545 9616). The publisher and the organizations appearing herein assume no responsibility for any injury and/or damage to persons or property as a matter of product liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of the rapid advances in the medical sciences, we recommend that independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the editors, publisher, or staff. The editors, publisher, and staff disclaim any responsibility for such material and do not guarantee, warrant, or endorse any product or service advertised in this publication nor do they guarantee any claim made by the manufacturer of such product or service.

Although all advertising material is expected to conform to ethical and medical standards, inclusion in this publication does not constitute a guarantee or endorsement by the Journal or its staff of the quality or value of such products or of the claims of any manufacturer. The paper used in this publication meets the minimum requirements of the American National Standard for Information Sciences Permanence of Paper for Printed Library Materials, ANSI Z39.48-1992.

© 2021 *Journal of Drugs in Dermatology*

BPA WORLDWIDE BUSINESS

Does molluscum keep him away from his friends?

Not representative of all patients

When left untreated, **symptoms last an average of 13 months and can last for as long as 4 years**.[1-3]

Many dermatologists believe that early treatment of molluscum may[1,2,4,5]:

- Reduce disease progression
- Control the number of lesions and decrease the potential for scarring
- Avoid the spread to other areas of the body or to other people
- Prevent onset and exacerbation of comorbidities such as atopic dermatitis
- Reduce discomfort and itching
- Prevent social exclusion from school or extracurricular activities
- Alleviate anxiety in children and caregivers
- Improve quality of life for patients

References: 1. Silverberg NB. Pediatric molluscum: an update. *Cutis*. 2019;104(5):301-305. **2.** American Academy of Pediatrics. Molluscum contagiosum. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2018:565-566. https://redbook.solutions.aap.org/redbook.aspx **3.** Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Time to resolution and effect on quality of life of molluscum contagiosum in children in the UK: a prospective community cohort study. *Lancet Infect Dis*. 2015;15(2):190-195. doi:10.1016/S1473-3099(14)71053-9 **4.** van der Wouden JC, van der Sande R, Kruithof EJ, Sollie A, van Suijlekom-Smit LW, Koning S. Interventions for cutaneous molluscum contagiosum (review). *Cochrane Database Syst Rev*. 2017;5:CD004767. doi:10.1002/14651858.CD004767.pub4 **5.** Silverberg NB. Pediatric molluscum contagiosum: optimal treatment strategies. *Pediatr Drugs*. 2003;5(8):505-512.

Copyright © 2020, Verrica Pharmaceuticals Inc. All rights reserved. (10/20) COMM75.01

VERRICA™ PHARMACEUTICALS
Reinventing Skin Science

NEXTSTEPS IN DERM

DERMATOLOGY CAREER RESOURCES AND CUTTING-EDGE INDUSTRY NEWS AT YOUR FINGER TIPS

Find practice management tips and career-building guidance from industry experts all in one place!

RESIDENT CORNER

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

PATIENT BUZZ SERIES

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

JDD CORNER

Editorial highlights each month from the Journal of Drugs in Dermatology (JDD), as well as podcasts and the "Ask the Investigator" series. PLUS, case reports and discussion on the most interesting cases highlighted in the *Journal of Drugs in Dermatology*

VIDEO CONTENT

Next Steps in Derm has a robost library of video pearls, webinars, virtual conferences, and the Translational Science Lecture Series. With new content being added regularly!

NextStepsInDerm.com

@NextSteps_Derm @nextstepsinderm @NextStepsinDerm Next Steps in Derm

Beauty is only skin deep

but **skin damage** can go much deeper

For samples or more information, please call (866) 668-7482

HELIOCARE®

Heliocare is a daily dietary supplement made with proprietary Fernblock® *Polypodium leucotomos* extract (PLE) technology. This clinically proven natural extract is packed with antioxidant properties that help maintain your skin's ability to protect itself against the aging effects of free radicals to help promote younger, more resilient-looking skin.*

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

doi:10.36849/JDD.6181

November 2021 1150 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Optimizing Outcomes With the 1550/1927 nm Dual Wavelength Non-Ablative Fractional Laser: Experienced User Recommendations

Paul M. Friedman MD,[a] Anne Chapas MD,[b] Suzanne L. Kilmer MD,[c] Zakia Rahman MD,[d] Wendy Roberts MD,[e] E. Victor Ross MD,[f] Jill S. Waibel MD,[g] Jeffrey S. Dover MD FRCPC[h]

[a]Dermatology and Laser Surgery Center, Houston, TX
[b]Union Square Laser Dermatology, New York, NY
[c]Laser & Skin Surgery Center of Northern California, Sacramento, CA
[d]Stanford University, Stanford, CA
[e]Rancho Mirage, CA
[f]Laser and Cosmetic Dermatology Center, Scripps Clinic, San Diego, CA
[g]Miami Dermatology and Laser Institute, Miami FL
[h]SkinCare Physicians, Chestnut Hill, MA

ABSTRACT

Background: Fractional laser treatment was introduced in 2004 as a non-invasive technique to treat sun-damaged and aging skin. Since then, numerous ablative and non-ablative photothermolysis technologies and devices have been introduced, increasing the options for clinicians and patients but also increasing the complexity regarding which system to use and the techniques to optimize outcomes. No two devices are the same and the user-manuals preset dosimetry does not address many clinical situations, which can create confusion for new and inexperienced users.

Methods: An online survey addressing use of a 1550 nm /1927 nm dual wavelength, non-ablative, fractional laser was sent to eight (8) US board certified dermatologists with extensive experience in the use of the device. The survey included 39 questions, addressing experience, best practices and recommendations for use.

Results: The survey data suggests that the device can be used to treat patients of all ages and skin types for indications including photoaging and photodamage, periorbital wrinkles, freckles, (ephelides), solar lentigines, poikiloderma, scarring due to acne or surgery. It can be used on both facial and non-facial areas, including neck, chest, hands, arms, abdomen, legs, and buttocks. Unexpected and adverse effects were rarely reported and those that did were mild and transient.

Conclusions: This position paper provides practical real-world guidelines resulting from a small survey of experienced users, for new and early uses of the novel 1550 nm /1927 nm dual wavelength, non-ablative, fractional laser.

J Drugs Dermatol. 2021;20(11):1150-1157. doi:10.36849/JDD.6181

INTRODUCTION

Skin resurfacing with laser devices has become a popular non-surgical rejuvenation option for photodamaged skin. Dermatologic lasers in common use include ablative and non-ablative devices in both fractionated and unfractionated forms as well as radiofrequency technologies. This article presents results of an online survey highlighting the best practices of physicians with collective experience of approximately 50,000 treatment procedures, using the fractionated, non-ablative dual wavelength 1550 nm erbium doped glass fiber/ 1927 nm thulium fiber laser (Fraxel Dual®, Solta Medical, Hayward, CA). Although the safety and efficacy of this device has been demonstrated in clinical studies[2-8] and in routine clinical practice since 2009, the multiple treatment setting options can be complex for new users.

These recommendations aim to simplify and provide real-world guidance in order to achieve optimal aesthetic outcomes.

Although we suggest how to optimize use of the 1550 nm/ 1927 nm dual wavelength, non-ablative, fractional laser, the recommendations should not replace an in-depth understanding of laser-tissue interactions, the technical user manual and hands-on training. Furthermore, the recommended techniques are applicable to the majority of patients, but each patient deserves customized treatment settings.

MATERIALS AND METHODS

The recommendations were developed from the results of a 39-question survey tool developed by Solta Medical and reviewed by the authors. Questions covered topics ranging

from demographic information, years of experience with the device, patient selection, body areas treated, treatment protocols, patient outcomes and tolerability. Where appropriate, indeterminate responses and "other" options were provided to ensure responses were fully captured. Because the survey was based on retrospective and subjective responses, it was classified as observational research and as such neither patient consent nor ethics board approvals were required.

The survey participants, eight geographically diverse, US-based board-certified dermatologists, were invited by the sponsor to participate in an online survey because of their extensive experience of the dual wavelength laser.

The survey was conducted between February 26 and April 2, 2020. An online questionnaire was distributed electronically by an independent market research organization. The online Survey Monkey tool (SurveyMonkey.com, Palo Alto, CA) was selected for its simplicity, scalability, immediate data capture and ease of analysis. Non-responders received automated weekly reminders until a 100% response rate was achieved. All responses were anonymous and were analyzed by an independent third party. All respondents received a stipend for their participation in the survey.

Data Analysis

Responses to multiple-choice questions were managed by SurveyMonkey.

Data from the multiple-choice questions were evaluated by response count and response percentage. Not all respondents answered all questions; therefore, the results were calculated according to responses to a particular question. A summary of anonymous responses was made available to all authors prior to preparation of the manuscript.

RESULTS

Respondent Demographics

All survey respondents (N=8) were board-certified dermatologists experienced in the use of fractionated non-ablative lasers.

Treatment Area Experience

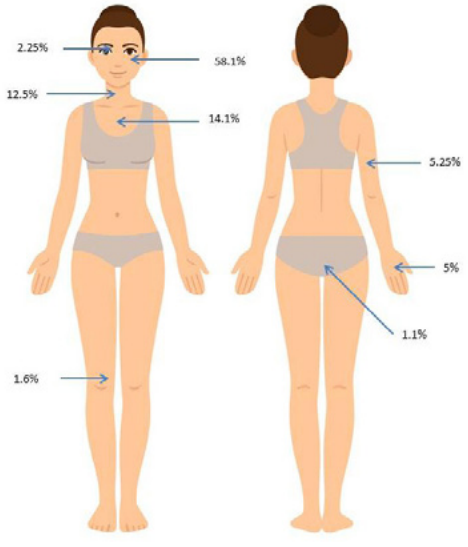
100% of respondents had treated patients with fractionated non-ablative lasers on the face, neck/submentum, and arms. The face was the most frequently treated area (58.1%). Chest/décolletage accounted for 14.1%, neck/submentum 12.5% and eyelids 2.25% of all treatments. Other areas of the body treated included: arms 5.25%, hands 5%, abdomen 1.8%, legs/knees 1.6%, and buttocks 1.1% (Figure 1).

Treatment Protocols

Patient Skin Types

The 1550 nm /1927 nm dual wavelength non-ablative fractional laser can be used to treat patients with all Fitzpatrick skin types. Skin types II and III were the most commonly treated by survey respondents.

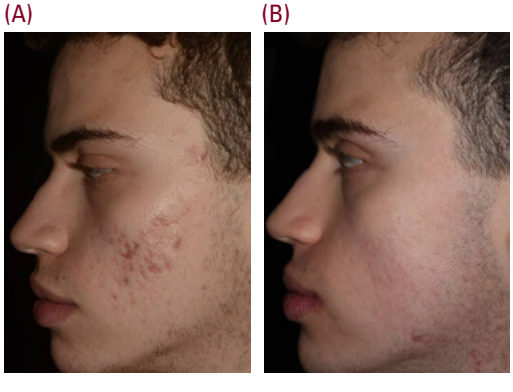
FIGURE 1. Treatment area experience.



Skin of Color

Fractional non-ablative laser treatments revolutionized the ability to treat skin of color. Within the responses, special consideration was given to the skin of color population as rebound hyperpigmentation and exacerbation of melasma can occur in some patients. Although all races and ethnicities are susceptible to photoaging, the increased epidermal melanin in Fitzpatrick skin types IV to VI provides a natural photoprotective effect, leading to delayed or less pronounced photoaging.[9-10] For these patients, the authors suggest using lower fluence and density settings when treating photoaging, and the 1927 nm wavelength with extra cooling between passes with ice or cool air. Acne scarring is more common in skin of color (Figure 2).[11]

FIGURE 2. Acne scarring in a 22-year-old male (A) Baseline. (B) After 5 treatments by vascular lasers and 1550 nm laser – 40 mJ / treatment level 8/4 passes. *Photo credit. Dr J Waibel.*



Black, Hispanic and Asian patients may achieve good results with higher fluence by utilizing lower densities to prevent post-inflammatory hyperpigmentation (PIH).

Additional recommendations for more experienced users include careful use of combination thulium 1927 nm and IPL with oral/topical tranexamic acid, topical hydroquinone, and good sun protection; priming skin with retinoids and/or bleaching agents, and post-treatment use of clobetasol followed by alternating tretinoin and hydroquinone.

Pre-Treatment Recommendations

The 1550 nm /1927 nm dual wavelength, non-ablative, fractional laser Technical User Manual recommends that patients should discontinue use of isotretinoin 6–12 months prior to treatment. The authors note that this advice has been refuted by both the American Society for Dermatological Surgery and a systemic evidence-based review both of which concluded that there is insufficient evidence to justify delaying treatment with non-ablative fractional devices in patients currently or recently exposed to isotretinoin.[12,13]

To achieve optimal results most authors, recommend that patients discontinue use of retinols, glycolic acid products, salicylic acid products, tanning, or sun exposure 2 weeks prior to and / or after laser treatment, and to stop waxing, abrasive scrubs, and microdermabrasion treatments 7–10 days prior to treatment.

Patients should be screened for a history of potential sensitivity to topical anesthetics and the clinician must be fully versed in the nature, presentation, and treatment of anesthesia toxicity. For patients with no contraindications to ester and amide forms of local anesthesia, planning to undergo treatment with the 1550 nm laser, a high concentration topical ie, 23% lidocaine/7% tetracaine, should be applied to the treatment area and adjacent border approximately 60–90 minutes beforehand. For the 1927 nm laser a lower concentration topical eg, 7% lidocaine/7% tetracaine can be used. The dose of lidocaine and tetracaine cream that provides effective local dermal analgesia depends on the duration of the application and the size of the area to be treated. When ready to treat, the local anesthetic should be removed with dry gauze or wipes, then the skin degreased with 70% rubbing alcohol, or witch hazel for sensitive skin, to ensure that the topical has been removed entirely so the laser will be absorbed by water in the dermis during treatment.

Wavelength Selection

The 1550 nm /1927 nm dual wavelength, non-ablative, fractional laser offers several treatment setting variables including wavelength, pulse energy (depth) and percentage of coverage (microthermal zones density [MTZ]), treatment level, number of passes, number of treatments, and time intervals between treatments. These options allow for use in superficial and deep indications, on all skin types and anywhere on the body. This enables experienced users the flexibility to precision tune the device to optimize treatment for each patient. However, the authors recognize that this versatility creates a learning curve for new users. For the majority of indications, preferred treatment settings have been empirically determined by experienced users. The following section aims to assist new users in simplifying these treatment decisions by providing broad guidance based on our shared experience of treating over 50,000 patients.

1550 nm Erbium-Doped Laser

The 1550 nm laser, with a depth range from 382–1359 micrometers The deeper depth of coagulation is primarily used for deeper resurfacing indications requiring collagen remodeling such as treatment of scarring due to acne or surgery, wrinkles, rhytids, and general skin resurfacing (Figure 3). It has a wide variety of pulse energy settings that can be tuned in accordance with the relative depth of the treatment indication. Higher energy settings are generally selected for deeper lesions, whereas when treating for pigment or tone, lower pulse energies should be used.

Respondents used the standalone 1550 nm erbium-doped laser 10–40% of the time (mean = 25%). The responses indicate that

FIGURE 3. Surgical scar on the wrist of a 77-year-old female. (A) Baseline. (B) After three treatments with vacular laser and thulium 1927 nm laser –20 mJ / treatment level 5/6 passes. *Photo credit. Dr J Waibel.*

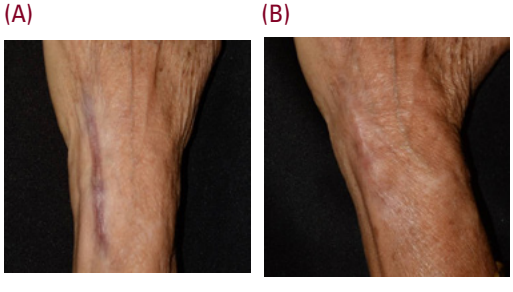
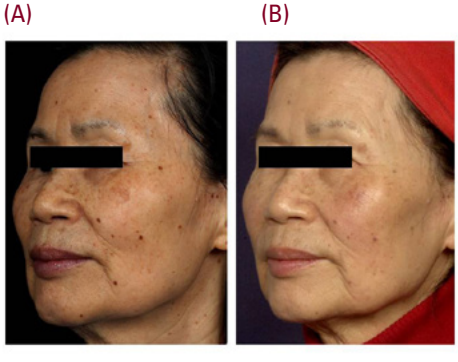


FIGURE 4. Melasma in skin of color. (A) Baseline (B) After 4 treatments. *Photo credit. Dr Z Rahman.*



the ideal candidate for the standalone 1550 nm includes those with: early, mild, moderate, and to a lesser extent, severe signs of aging /sun damage. 100% of respondents used it to treat acne scars and surgical scars, 75% used to treat periorbital wrinkles, 62.5% to treat melasma, and 50% to treat lentigines, solar lentigines, and actinic keratoses (Figure 4). Additionally, one respondent reported using it off label for treatment of burn and trauma scars and post-inflammatory hyperpigmentation.

Patients of all age groups can be treated with the 1550 nm erbium-doped laser. Respondents reported treating patients aged 20–60, with those in their 30's and 40's being treated most frequently.

Many variables exist, including the nature and severity of the condition being treated, skin type, and willingness for downtime; however, there was no agreed protocol for the number of treatments recommended for the standalone 1550 nm erbium doped laser. Given the fractional nature of the treatment, the number of treatments recommended per patient ranged from 2–6. Treatments are typically at 4–6-week intervals at the minimum, but there is no presumed loss of efficacy if longer treatment intervals are desired. For darker skin types, the interval may be 6–8 weeks along with use of a post-operative skin brightener. Treatment number depends on severity of initial condition.

1927 nm Thulium Laser

The 1927 nm wavelength targets superficial resurfacing and pigmented lesions as it provides superficial penetration (192–202µm) to target the epidermis, basal layer epidermis where the melanocytes reside, and the upper level of the papillary dermis. Respondents used the 1927 nm thulium laser setting 10–75% of the time (mean = 33.1%)

The ideal candidate for the standalone 1927 nm thulium treatment includes early, mild, moderate, and severe signs of aging and sun damage, with or without actinic keratoses. One respondent reported using it 'off-label' in PIH and other conditions associated with pigmentation such as lichen planus pigmentosus and melasma (Figure 5).

Half the respondents generally recommend 2–3 initial treatments, 37.5% recommend 1–2 treatments, and 1 respondent reported recommending 3–4 treatments. All respondents recommended maintenance treatments 1–2 times per year following the initial series.

The mean percentage of patients treated using the standalone 1927 nm laser were, by age group: 20's–5%; 30's–20%; 40's–27.5%; 50's–25%; 60's or older–22.5%.

1550 nm/1927 nm Dual Wavelength

7 of 8 experienced users combine 1550 + 1927 nm lasers during the same session or on the same body area in 20–60% of their patients (mean = 47.8%).

The primary reason respondents selected the 1550 nm/1927 nm dual wavelength laser system over other laser systems is the consistent efficacy. Other reasons cited by over 80% of respondents included the ability to treat multiple skin types, the ability to treat multiple body areas in one session, and its demonstrated safety profile.

87.5% of respondents stated the ideal candidate for combination 1550 nm and 1927 nm treatment is someone with moderate signs of aging/sun damage or scarring. 50% supported its use in early and mild photoaging and 37.5% in patients with severe aging/sun damage or scarring.

The mean percentage of patients treated by survey respondents using the combination 1550 nm and 1927 nm laser by age group: 20's–5.7%; 30's–14.3%; 40's–26.4%; 50's–28.6%; 60's or older–26.4%.

Combining 1550 + 1927 nm Laser System With Other Treatments

All respondents used the 1550nm/1927 nm dual wavelength laser system in combination with a range of other treatment modalities including Q-switched 755 nm alexandrite laser, 532 nm wavelength lasers, 1450 nm diode lasers, pulsed dye lasers, frequency doubled neodymium YAG pigmentation lasers, neuromodulators, dermal fillers, chemical peels, intense pulsed light devices, non-microneedling monopolar radiofrequency, and radiofrequency microneedling (Figure 6).

FIGURE 5. PIH in a 17-year-old Hispanic male (A) Baseline (AB) After 5 treatments with the 1927 nm laser – 15 mJ / treatment level 5/ 5 passes. *Photo credit: Dr J Waibel.*

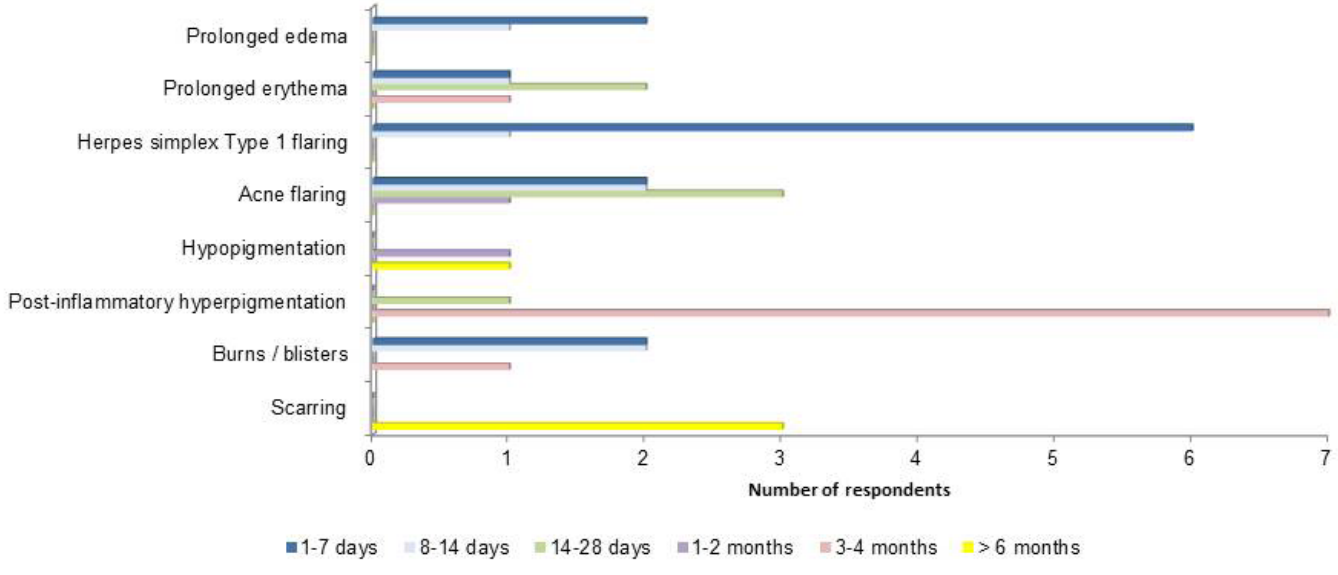
(A) (B)

FIGURE 6. What other treatments do you combine with the 1550 nm/1927 nm dual wavelength laser?

Adjuvant Treatment	Responses	%
Neurotoxins	7	87.5
Dermal Fillers	6	75
Other energy-based devices*	6	75
Non-invasive radiofrequency	4	50

*RF microneedling, Q-Switched Alexandrite Laser, Pulsed Dye Laser (PDL), Excel V Laser, non-ablative fractional laser (NAFL), Intense Pulsed Light (IPL), ablative fractional laser (AFL), Pico Laser, Liquid Nitrogen (LN2), Plgmentation Laser

FIGURE 7. Time to resolution of unexpected outcomes.



Respondents used the 1550 nm/1927 nm dual wavelength laser system both before and after the above-mentioned treatment modalities based on both personal preference and the patient's tolerance to pain.

There was significant variance on how long to wait before injecting dermal fillers after treatment with the 1550 nm/1927 nm dual wavelength laser, ranging from immediately to at least one month, while others recommended that if filler is administered on day of treatment, then it should be injected prior to laser treatment. Similarly, respondents provided wide-ranging responses on the wait before injecting neurotoxins from immediately before laser treatment to minutes afterwards, (with caution and after skin cooling) to 1-week post laser treatment.

Of the 4 respondents who use noninvasive radiofrequency (Thermage FLX®, Solta, Hayward, CA) in combination with the 1550 nm/1927 nm dual wavelength laser there was general agreement that noninvasive radiofrequency should be done first. Laser treatment should be done within 1–3 months.

87.5% of respondents use other energy-based treatments in combination with the 1550 nm/1927 nm dual wavelength laser. Of these, five perform the procedures on the same day, while two suggest waiting 1–2 weeks or until healing is complete.

Post-Treatment

Immediately post-treatment, ice packs or a cryotherapy cooled air device should be used to reduce heat sensation and aid patient comfort. Patients should be instructed to avoid injury and sun exposure to the treated area for 2–4 weeks and to use a high SPF sunscreen (at least SPF 30) daily.

All respondents recommend the use of post-treatment moisturizer/ post-laser ointment until all microscopic epidermal necrotic debris (MENDS) have healed as well as elevating the head of the bed for 24–48 hours or until edema has completely resolved. Icing and avoidance of vigorous exercise and sunlight were also recommended (Figure 7).

Treatment Outcomes

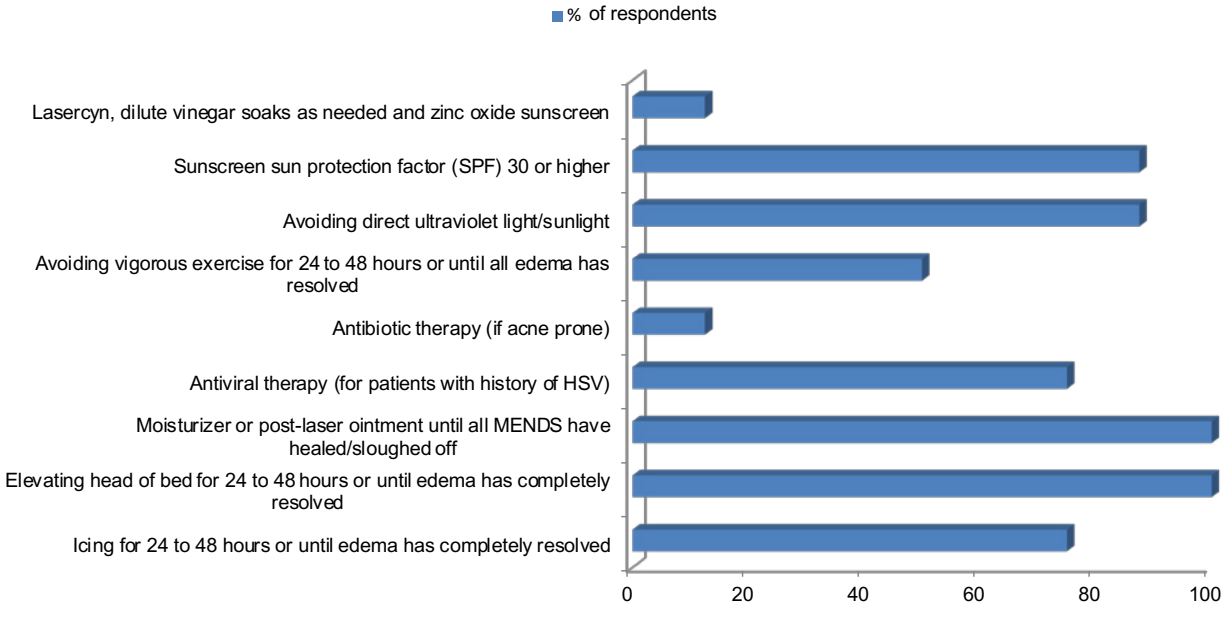
6 of 8 respondents stated that 75–100% of patients achieve improvement following treatment with the 1550 nm/1927 nm dual wavelength laser regardless of the wavelength or combination treatment protocol. Two felt that 51–74% of patients improve. Of note, one author commented "Excellent for non-ablative rejuvenation in younger patients."

Unexpected Outcomes

Unexpected outcomes were rare. They were reported in <1% of patients by 5:8 respondents (62.5%); in 2–5% by 2:8 (25%) and in 6–10% of patients by 1:8 (12.5%) [mean = 1.9%]. Of these, all reported them to be mild and temporary, resolving within days to months of treatment (Figure 7). The most commonly reported adverse outcomes were acne flaring and PIH (Figure 8). This is consistent with data reported by other authors.[14,15,16]

Side effects can be minimized by the use of post-treatment moisturizers or post-laser ointment until all MENDS have healed. Other strategies include elevating the head of the patient's bed, icing, and advising avoidance of vigorous exercise for 24–48

FIGURE 8. Post-treatment instructions.



hours or until edema has completely resolved, along with ongoing use of high SPF sunscreen, and avoidance of sunlight. Oral antibiotics, typically the tetracycline drug class, starting on the day of treatment can minimize the risk of acne flaring.

DISCUSSION

This is the first survey of US dermatologists to evaluate experience and develop recommendations for new users of the 1550/1927 nm Dual Wavelength Fractional Laser system. While relatively simple in design and limited in scope, it captured critical points regarding practical real-world usage. These data confirm that the device can be used to treat patients of all ages and skin types for indications that include photoaging and photodamage, discoloration of the skin, as well as periorbital wrinkles, freckles, and scarring due to acne or surgery (Figure 9).

FIGURE 9. Melasma in a 40-year-old Hispanic female (A) Baseline. (B) After 2 treatments with IPL and 1927 nm laser. *Photo credit. Dr J Waibel.*

(A) (B)

As shown in other studies[2,5-8] the device can be used on both facial and non-facial areas, including neck, chest, hands, arms, abdomen, legs, and buttocks.

Skin types IV–VI generally require less energy and treatment density to reduce the risk of PIH.

Additionally, energy/density settings should be reduced for off the face indications given the reduced oil gland density of the skin.

For new users of the 1550/1927 nm dual wavelength fractional laser system, the variety of treatment parameter options can be overwhelming. The authors suggest that new users can simplify the decision tree and achieve the highest benefit:risk ratio by selecting treatment settings based on the following 4-step algorithm:

Step 1. Select the wavelength based on indication you are treating, aiming for deep (1550 nm) or superficial (1927 nm) or both types of treatment

Step 2. Determine the depth of target and tune the mJ to corresponding depth

Step 3. Identify the patient's skin type (I–III or IV–VI) and consider decreasing density for types IV– VI

Step 4. Choose the body area to be treated (face, eyes or 'off face'), if treating off face consider decreasing both depth and density

In addition, the following general treatment principles and settings, based on our combined experience, may help to guide new users.

For melasma, and darker skin patients 5 mJ / treatment level 2 using the 1927 nm wavelength.
For lighter skin and diffuse dyschromia, 10 mJ /treatment level 7, using the 1927 nm wavelength.
For off-the-face pigmentation 10 mJ / treatment level 4 or 3, using the 1927 nm wavelength.
For acne scars 40–50 mJ /treatment level 7, using the 1550 nm wavelength, regardless of skin type, unless the patient has melasma, in which case lower the settings to 10 mJ / treatment level 3 or 4 / 1550 nm, and augment with 1927 nm / 5 mJ / treatment level 2.
For general rejuvenation, 30 mJ / treatment level 4 with 1550 nm, followed by 10 mJ / treatment level 4 with 1927 nm.

Unexpected and adverse effects were rarely reported by the experienced user survey participants and those that did were mild and transient. This is consistent with previously reported data showing that fractional laser skin resurfacing with the 1550 nm/1927 nm dual wavelength laser is associated with a relatively low complication rate compared to other skin rejuvenation procedures.[17-19]

A retrospective study of 856 treatments in 362 Asian patients with skin phototypes III–IV treated at a single center revealed an adverse event rate of 5%.[17] The most frequently reported complications were prolonged erythema (1.8%), PIH (1.1%), and aggravation of melasma (0.9%). Less frequently observed adverse events included herpes simplex outbreak (0.6%) and acneiform eruption (0.2%). There were no reports of long-term adverse events.

Another retrospective chart review of 730 patients with Fitzpatrick skin types I–IV reported an overall complication rate of 4.2%. There was no significant difference in the rate of complications among the patients treated with either the 1550 nm or 192 7nm laser. Complications were generally minor, and all resolved completely with treatment.

Complications included HSV breakouts, acne eruptions, abrasion, bacterial infection, dermatitis, drug eruption, prolonged erythema, hyperpigmentation, increased swelling and telangiectasia. There was no significant relationship between Fitzpatrick skin type and incidence of complications (P=0.37).[18]

A third study of 961 consecutive 1,550 nm erbium-doped laser treatments on 422 consecutive patients with skin phototypes I–V, showed a complication rate of 7.6%.[18] The most frequent were acneiform eruptions, HSV outbreak and erosions. Less frequent side effects included PIH, prolonged erythema, prolonged edema and dermatitis. As seen with other skin resurfacing procedures, complications were significantly more frequent in those with darker skin phototypes (2.16 vs 2.02, P=0.0071).

LIMITATIONS

The findings of this survey have to be seen in light of some limitations. Chief among these are that it relied on self-recall/reporting and it included only a small number of highly-selected participants. Originally it was intended to develop Consensus Guidelines based on a live, experienced-user round table meeting. However due to the COVID-19 pandemic, this event had to be cancelled, necessitating the change in scope and methodology.

Neither individual questions, nor the entire questionnaire was pre-tested or validated, so it is possible that important data was not captured, compromising the survey's validity.

The survey design did not require that all participants answer all questions resulting in some missing data, although as the sample size did not permit statistical analysis, the effect of missing data had minimal effect on overall analytics.

Although the number of respondents was small, as there are reported to be approximately 700 1550 nm/1927 nm dual wavelength laser systems in the US,[20] the eight respondents represent 1.14% of the total potential sample population, so may be considered a representative sample, even if the numbers are not sufficient for meaningful statistical analysis.

Potential commercial influence is a possibility as the questions were developed by the device manufacturer, however the company was not involved in data analysis, manuscript development, or review. Furthermore, the survey was developed based on common questions received from clinicians on the practical uses of the device, rather than issues of commercial interest.

Additionally, there was participant sample bias as survey respondents were selected for their extensive experience 1550 nm/1927 nm dual wavelength laser system. Moreover, they were compensated for their participation in the survey and subsequently became the manuscript authors. While this has the inherent potential for bias it also had the advantage that there was no misinterpretation of the data.

Finally, despite the fact that surveys are common in health care research, there is a lack of guidance on the reporting of such research to medical journals.[21]

These limitations should be addressed in future studies. We recommend a prospective survey of all 1550 nm/1927 nm dual wavelength laser system users exploring typical usage, treatment parameters, clinical outcomes, and complications.

Additionally, comparative experience with other ablative and non-ablative devices could be included.

DISCLOSURES

Dr. Anne Chapas is a Consultant to Solta Medical.
Dr. Jeffrey Dover is a Consultant to Solta Medical.
Dr. Paul Friedman is a Consultant to Solta Medical
Dr. Suzanne Kilmer previously received research support and was a member of Solta's Medical Advisory Board.
Dr Zakia Rahman is a Consultant to Solta Medical.
Dr. Wendy Roberts is a Consultant to Solta Medical and a member of their Medical Advisory Board.
Dr Edward Ross serves on Solta Medical's scientific advisory board.
Dr. Jill Waibel is a Consultant to Solta Medical.

Financial Disclosures and Products: The survey and Ms. Miller's work were financially supported by Solta Medical, Hayward CA. The sponsor had no role in the conduct of the survey, interpretation of the data, nor in the preparation, review or approval of the manuscript. No honoraria or other forms of payment were made for authorship of this article.

ACKNOWLEDGMENT

The authors would like to thank Pooja Sodha MD for her expert review and revision of the manuscript and Judi Miller of Strategic Pharmaceutical Advisors, McLean VA for assistance with manuscript preparation.

REFERENCES

1. Cohen SR, Goodacre A, Lim S, et al. Clinical outcomes and complications associated with fractional lasers: a review of 730 patients. *Aesthetic Plast Surg*. 2017;41(1):171-178.
2. Narukar VA, Alster TS, Bernstein EF, Lin TJ, Loncaric A. Safety and efficacy of a 1550 nm/1927 nm dual wavelength laser for the treatment of photodamaged skin. *J Drugs Dermatol*. 2018;17(1):41-46
3. Beasley KL, Weiss RA. Nonablative fractional lasers. In: Goldman MP, Fitzpatrick RE, Ross EV, Kilmer SL, Weiss RA eds. Lasers and Energy Devices for the Skin. *CRC Press*. 2013:178-191
4. Tanzi EL, Wanitphakdeedecha R, Alster TS. Fraxel laser indications and long-term follow-up. *Aesthet Surg J*. 2008;28(6):675–678, discussion 679–680.
5. Brauer JA, McDaniel DH, Bloom BS, Reddy KK, Bernstein LJ, Geronemus RG. Nonablative 1927 nm fractional resurfacing for the treatment of facial photopigmentation. *J Drugs Dermatol*. 2014;13(11):1317-1322. PMID: 25607696.
6. Weiss ET, Brauer JA, Anolik R, et al. 1927 nm fractional resurfacing of facial actinic keratoses: a promising new therapeutic option. *J Am Acad Dermatol*. 2013;68(1):98-102. doi:10.1016/j.jaad.2012.05.033
7. Polder KD, Harrison A, Eubanks LE, Bruce S. 1,927 nm fractional thulium fiber laser for the treatment of nonfacial photodamage: a pilot study. *Dermatol Surg*. 2011;37(3):342-348. doi:10.1111/j.1524-4725.2011.01884.x
8. Polder KD, Bruce S. Treatment of melasma using a novel 1,927 nm fractional thulium fiber laser: a pilot study. *Dermatol Surg*. 2012;38(2):199-206. doi:10.1111/j.1524-4725.2011.02178.x
9. Griffiths CE, Goldfarb MT, Finkel LJ, et al. Topical tretinoin (retinoic acid) treatment of hyperpigmented lesions associated with photoaging in Chinese and Japanese patients: a vehicle-controlled trial. *J Am Acad Dermatol*. 1994;30:76-84.
10. Alexis AF, Rossi A. Photoaging in skins of color. *Cosmetic Dermatol*. 2011;24(8):367-370.
11. Halder R.M.Ara C.J.Skin cancer and photoaging in ethnic skin. *Dermatol Clin*. 2003; 21 (x): 725-732
12. Waldman A, Bolotin D, Arndt KA, Dover JS, Geronemus RG, Chapas A, Iyengar S, Kilmer SL, Krakowski AC, Lawrence N, Prather HB, Rohrer TE, Schlosser BJ, Kim JYS, Shumaker PR, Spring LK, Alam M. ASDS Guidelines Task Force: Consensus recommendations regarding the safety of lasers, dermabrasion, chemical peels, energy devices, and skin surgery during and after isotretinoin use. *Dermatol Surg*. 2017;43(10):1249-1262
13. Spring LK, Krakowski AC, Alam M, Bhatia A, Brauer J, Cohen J, Del Rosso JQ, Diaz L, Dover J, Eichenfield LF, Gurtner GC, Hanke CW, Jahnke MN, Kelly KM, Khetarpal S, Kinney MA, Levy ML, Leyden J, Longaker MT, Munavalli GS, Ozog DM, Prather H, Shumaker PR, Tanzi E, Torres A, Velez MW, Waldman AB, Yan AC, Zaenglein AL. Isotretinoin and Timing of Procedural Interventions: A Systematic Review With Consensus Recommendations. *JAMA Dermatol*. 2017 Aug 1;153(8):802-809. doi: 10.1001/jamadermatol.2017.2077. PMID: 28658462.
14. Rho N. Short- and long-term side effects of non-ablative fractional laser resurfacing in Koreans: Analysis of 286 consecutive treatments. *Medical Lasers*. 2014;3:17-21.
15. Taub, A.F. The treatment of acne scars, a 30-year journey. *Am J Clin Dermatol*. 2019;20:683–690.
16. Chan, N.P., Ho, S.G., Yeung, C.K., Shek, S.Y. and Chan, H.H. (2010), The use of non-ablative fractional resurfacing in Asian acne scar patients. *Lasers Surg. Med*. 42: 870-875. doi:10.1002/lsm.20976
17. Lee SM, Kim MS, Kim YJ, Won CH, Lee MW, Choi JH, Moon KC, Chang SE. Adverse events of non-ablative fractional laser photothermolysis: a retrospective study of 856 treatments in 362 patients. *J Dermatolog Treat*. 2014 Aug;25(4):304-7.
18. Cohen SR, Goodacre A, Lim S, Johnston J, Henssler C, Jeffers B, Saad A, Leong T. Clinical outcomes and complications associated with fractional lasers: a review of 730 patients. *Aesthetic Plast Surg*. 2017 Feb;41(1):171-178.
19. Graber EM, Tanzi EL, Alster TS. Side effects and complications of fractional laser photothermolysis: experience with 961 treatments. *Dermatol Surg*. 2008 Mar;34(3):301-5; discussion 305-7.
20. Solta Medical, Hayward, CA. Data on File.
21. Bennett C, Khangura S, Brehaut JC, Graham ID, Moher D, Potter BK, Grimshaw JM. Reporting guidelines for survey research: an analysis of published guidance and reporting practices. *Plos Med* 2011.https://doi.org/10.1371/journal.pmed.1001069.

AUTHOR CORRESPONDENCE

Paul M. Friedman
E-mail:..... drpaul@dermlasersurgery.com

SKYRIZI IS NOW AVAILABLE AS A SINGLE 150 mg INJECTION

For adults with moderate to severe plaque psoriasis

1 INJECTION 4 TIMES A YEAR[1]

After Week 0 and 4 Injections

Skyrizi®
risankizumab-rzaa

SKYRIZI is the only 4-dose-a-year biologic in psoriasis that offers a single-dose pen[1]

- **Same SKYRIZI you know and trust, now in a single 150 mg/mL injection[1]***
- **Consistent efficacy and safety profile[1-2]**
- **In-office or at-home administration after proper training[1]**

SKYRIZI is also available in a 150 mg/mL prefilled syringe

*Bioequivalence was demonstrated between a single 150 mg/mL injection and two 75 mg/0.83 mL injections in a prefilled syringe. Bioequivalence was also demonstrated between 150 mg/mL prefilled syringe and prefilled pen.[3]

ADMINISTRATION INSTRUCTIONS[1]

SKYRIZI is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SKYRIZI after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI according to the Instructions for Use.

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

Infection

- SKYRIZI® (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.
- In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Pre-Treatment Evaluation for Tuberculosis (TB)

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

Administration of Vaccines

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

Adverse Reactions

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

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

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

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Data on file, ABVRRTI71470. AbbVie Inc. **3.** Lon HK, Cheng L, Nudurupati S, et al. Pharmacokinetic comparability of risankizumab formulations in prefilled syringe and auto-injector for subcutaneous injection. *Clin Ther.* 2021;43(3):629-636. doi:10.1016/j.clinthera.2021.01.009

©2021 AbbVie Inc. North Chicago, IL 60064 US-SKZ-210068 May 2021 Printed in U.S.A.

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

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infections

SKYRIZI may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the SKYRIZI group compared to 14.7% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections and tinea infections occurred more frequently in the SKYRIZI group than in the placebo group. Subjects with known chronic or acute infections were not enrolled in clinical studies *[see Adverse Reactions]*.

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

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

Tuberculosis

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

Administration of Vaccines

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

ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

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

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

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

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

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

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

Specific Adverse Drug Reactions

Infections

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

Safety Through Week 52

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

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women with plaque psoriasis who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161.

Risk Summary

Limited available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. At the 50 mg/kg dose [20 times the maximum recommended human dose (MRHD); 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual], increased fetal/infant loss was noted in pregnant monkeys *(see Data)*. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

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

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg (20 times the MRHD, based on mg/kg comparison) and the NOAEL for developmental toxicity was identified as 5 mg/kg (2 times the MRHD, based on mg/kg comparison). In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of SKYRIZI in pediatric patients less than 18 years of age have not yet been established.

Geriatric Use

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

OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab-rzaa (at 20 times the clinical exposure at the MRHD, based on mg/kg comparison) once weekly for 26 weeks.

PATIENT COUNSELING INFORMATION

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

Infections

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

Administration of Vaccines

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

Administration Instruction

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

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

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

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women with plaque psoriasis exposed to SKYRIZI during pregnancy and patients can call 1-877-302-2161 *[see Use in Specific Populations]*.

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA
US License Number 1889
SKYRIZI® is a registered trademark of AbbVie Biotechnology Ltd.
© 2019-2021 AbbVie Inc.
Ref: 20067753-R2 Revised: April, 2021

LAB-4850 **MASTER**

US-SKZ-210068

abbvie

doi:10.36849/JDD.6550

November 2021 1161 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Laser in the Treatment of Granulomas on the Nose Produced by Polymethylmethacrylate: A Case Series

Alberto Goldman MD,[a] Uwe Wollina MD,[b]
Denise Cantrelli Machado PhD,[c] Daniel Rodrigo Marionwic PhD[d]

[a]Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil
[b]Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Dresden, Germany
[c]Preclinical Research Center of Brain Institute of Rio Grande do Sul (BraIns), Pontifical Catholic University of Rio Grande do Sul (PUCRS) Porto Alegre, Rio Grande do Sul, Brazil
[d]Precision Medicine and Biotechnology Laboratory - Brain Institute of Rio Grande do Sul (BraIns) Porto Alegre, RS, Brazil

ABSTRACT

Background: The search for aesthetic non-surgical procedures is growing. The use of polymethylmethacrylate (PMMA) as a filling material in the nose represents one of the many options among these aesthetic procedures. Its use, however, can lead to complications. The treatment of these complications is often challenging.

Methods: We performed a retrospective clinical analysis of the medical records of patients undergoing treatment of PMMA granulomas of the nose at a private clinic from January, 2015, to January, 2021. A short-pulsed neodymium-YAG (Nd:YAG) laser was applied intranasally or directly by cutaneous incision in the granulomas. Laser-tissue interaction heats the alloplastic material, fragments the product and creates cleavage paths, thereby facilitating the removal of PMMA, either by intercartilaginous removal or aspiration.

Results: Twenty-seven patients were included in the study. All had a history of PMMA injection in the nose. All patients were treated with an intralesional pulsed 1064nm Nd:YAG laser. The material removed after laser-tissue interaction was sent for histopathological examination; this showed the presence of microparticles of exogenous material compatible with PMMA. The partial removal of the alloplastic material was shown to be effective in all cases. One patient developed a small blister in the nasal dorsum. Follow-up ranged from six to 47 months.

Conclusions: The use of intralesional Nd:YAG laser for the treatment of PMMA granulomas on the nose proved to be an effective and safe procedure with improvement of nasal shape, without compromising respiratory function. This technical option represents yet another alternative in the treatment of PMMA granuloma complications.

J Drugs Dermatol. 2021;20(11):1161-1166. doi:10.36849/JDD.6550

INTRODUCTION

Non-surgical procedures aimed at rejuvenating and improving the appearance of the face and nose have grown in recent years. They seek an effective result, a reduction in risks or complications and a shorter recovery period compared to surgery.[1] Among these options, injectable fillers have been increasingly used. They aim to correct folds or wrinkles, increase volume, and attenuate the signs of aging.[2] The appeal of fillers is that they are simple, low-cost and have a quick recovery when used for aesthetic treatment or nasal deformities.[1]

Fillers can be temporary (degradable), such as hyaluronic acid, semi-permanent like calcium hydroxylapatite, or permanent (non-degradable), such as polymethylmethacrylate (PMMA). The latter is composed of microspheres suspended in different vehicles such as bovine collagen or methylcellulose.[3] Temporary fillers need periodic reapplication to maintain the result. Although initially shown to be safe for soft tissue augmentation, adverse events (AEs), especially with permanent materials such as PMMA, have been unpredictable, sometimes severe, and difficult to handle in the medium and long term. These complications may occur early when they appear up to two weeks after application. Late complications develop during or after the first year following filler injection.[4–6]

The use of permanent fillers in the nose carries the risk of several severe adverse reactions such as vascular compromise, skin necrosis, and extrusion. Removing this material from the nasal structure is always difficult.[7] Foreign body nodules and granulomas are the most frequent manifestations. The main resources used in the management of adverse reactions related to PMMA are its surgical removal, aspiration, injection of corticosteroids, and intralesional laser (diode and Nd:YAG).[8–12]

In this article, we report a series of patients with PMMA granulomas in the nose and their treatment with intralesional 1064nm Nd:YAG laser.

MATERIALS AND METHODS

This project was approved by the Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul under Certificate of Presentation of Ethical Appreciation (CAAE 26778719.3.0000.5336 and opinion No. 3,786,448). Twenty-seven patients treated at a private clinic from January, 2015, to January, 2021, with complete medical records and history of PMMA injection in the nose, were included in the study (Table 1). The age ranged from 26 to 62 years (mean of 40.5); three patients were males (11.1%) and 24 were females (88.9%). All had granulomas in the nose. None of the patients had a history of previous surgical treatment on the nose. Patients with incomplete medical records or those with no opportunity of postoperative follow-up were excluded.

The evaluation of patients included detailed clinical and autoimmune history, and imaging techniques such as computed tomography, magnetic resonance tomography, or diagnostic ultrasonography. Imaging demonstrated the presence of alloplastic material in the nasal region, compatible with PMMA. All laser procedures were performed in a hospital environment, under local anesthesia and sedation, and accompanied by an anesthesiologist. The patients underwent treatment using a short pulse 1064nm Nd:YAG laser with a 633nm (red) diode laser aiming beam (Smartlipo, DEKA, Calenzano, Italy). Through an intercartilaginous incision, the cannula containing the optical fiber was introduced into the nose in direct contact with the granuloma. The duration of action and the amount of energy emitted by the laser was adapted to the individual findings. Twenty-five patients (91.3 %) had PMMA only in the region of the nasal dorsum. In these cases, the laser was directed at the subdermal and bony-cartilaginous planes, creating a cleavage between granuloma, nasal skin, and bony-cartilaginous vault. When PMMA was in the columella, tip or glabella, access was performed through a small puncture in the skin and, again, the optical fiber was introduced directly into the granuloma.

Before starting the laser procedure, the skin on the nose was cooled using cold compresses. To reduce the risk of thermal injury, the temperature of the treated area was controlled by a digital thermometer. The laser was deactivated whenever the skin temperature reached 42°C, at which time the region was cooled again with cold compresses. The laser energy acted on the granuloma in order to heat and fragment the alloplastic material. In addition, a subcutaneous and tight cartilaginous or bone separation (cleavage) path was created, facilitating the removal of fragments of PMMA from the nose. The transillumination obtained by a pilot diode laser beam worked as a guide. The reddish color visible on the skin surface accurately reflects the location and depth of the tip of the optical fiber. The more intense the red coloring, the more superficial is the tip of laser fiber, and thus the energy being emitted (Figure 1). During the procedure, the nose was frequently cooled using cold compresses. The power ranged from 9 to 16W, frequency from 40 to 60Hz, and pulse duration was 150µsec. In all cases, a 600µm optical fiber was used. The accumulated energy used in each case varied according to granuloma dimension and tissue resistance from 3.000 to 8.000 J. When the access was intercartilaginous, the intranasal incision was closed with 5-0 chromic catgut in the mucosal flaps. Immobilization of the nose was accomplished with porous adhesive tape

TABLE 1.

Summary of Patients Treated

Case	Gender	Age	Injected region	Months between initial application and onset of symptoms	Follow-up in months
1	Female	37	Dorsum	60	9
2	Male	42	Dorsum	50	14
3	Female	38	Dorsum	52	24
4	Female	33	Dorsum	27	21
5	Female	29	Dorsum	37	7
6	Male	42	Dorsum	19	8
7	Female	31	Dorsum	20	6
8	Female	37	Dorsum, tip and glabella	14	20
9	Female	50	Dorsum	72	47
10	Female	57	Dorsum	144	36
11	Female	29	Dorsum	18	38
12	Female	61	Dorsum	60	14
13	Female	38	Dorsum	24	18
14	Female	41	Dorsum	58	9
15	Female	26	Dorsum	102	30
16	Female	47	Dorsum	44	6
17	Female	44	Dorsum, tip and glabella	20	8
18	Female	62	Dorsum	48	6
19	Female	37	Dorsum	16	6
20	Female	58	Dorsum	39	12
21	Female	47	Dorsum	24	6
22	Female	33	Dorsum	48	24
23	Female	39	Dorsum	20	10
24	Female	28	Dorsum	12	6
25	Female	41	Dorsum	23	14
26	Male	38	Dorsum	16	24
27	Female	29	Dorsum	48	10

and a thermoplastic plate. All procedures were performed on an outpatient basis by the same surgeon. Patients were discharged from the hospital a few hours after recovery from anesthesia and sedation. The removed fragments were sent for histopathological examination. Postoperative care included analgesia, antibiotic prophylaxis and cold compresses.

RESULTS

Twenty-seven patients with granulomas in the nose related to the previous implantation of PMMA underwent treatment with intra-lesional laser (Table 1). The majority of patients were females (88.9 %). The period between initial application and onset of symptoms varied from 12 to 144 months (mean 41.29 months). In 25 cases, unilateral intercartilaginous access was chosen to introduce the cannula and optical fiber. In addition, two patients (7.4 %) were treated also by small incisions in the glabella and nasal tip. In these cases, the optical fiber was introduced without the cannula and acted in direct contact with the granuloma (Figure 2). After the laser application, the granuloma and fragments were removed using an aspiration probe or mechanical removal with forceps. All patients had some degree of edema and ecchymosis. One patient developed a small blister in the nose immediately after the procedure (3.7%). This postoperative side effect was treated with steroid and moisturizing creams with no cicatricial sequel or alteration in skin color. There was no case of bleeding, vascular alteration, embolization, dyspigmentation, or infection. One patient had to undergo further surgery to remove more material nine months after the initial procedure. Three patients who experienced breathing difficulties before the procedure reported improvement in the post-treatment period. The procedure was safe and effective. The aesthetic appearance resulted in a natural look after surgery (Figures 3–10). Patients who had neovascularization before the procedure, due to a reactive inflammatory process, showed a significant improvement in

FIGURE 1. YAG laser in subdermal granuloma on the nasal dorsum. A reddish coloration is observed by transillumination showing the exact position of the laser action.

FIGURE 2. Optical fiber introduced in the glabella.

FIGURE 3. Deformities and superficial vessels in the nose. History of application of PMMA five years ago.

FIGURE 4. Preoperative computed tomography showing the presence of alloplastic material, compromising the nasal structure.

FIGURE 5. Important attenuation of the vascular aspect and deformities nine months after treatment.

FIGURE 6. Same patient, tip and columella involvement and abundant superficial vascularization are observed.

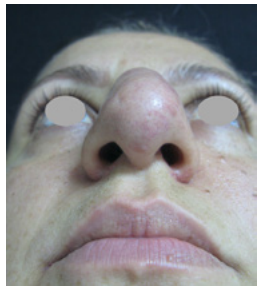


FIGURE 7. Result nine months after treatment of granuloma with intralesional laser.

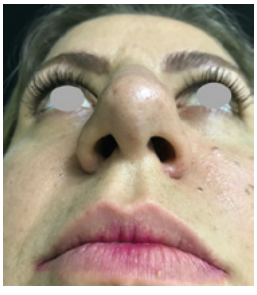


FIGURE 8. Fragments of granulomatous tissue removed from the dorsum and nasal tip after the action of the intra-nasal laser.

FIGURE 9. Irregularities and granuloma in the nasal dorsum after previous application of PMMA 8 years ago.

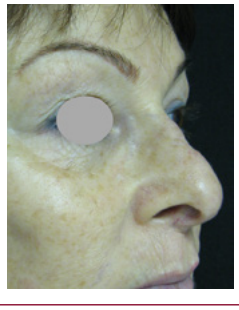
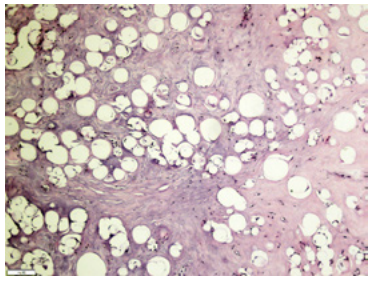


FIGURE 10. Result eight months after laser treatment with improved aesthetic appearance.

this aspect after the partial or total removal of the product. In one patient, the increase in volume that occurred 12 years after

FIGURE 11. Histopathological examination of the patient showing granulomatous infiltrate with histiocytes phagocyting small spherical structures. Fibrosis and surrounding lymphocytic infiltrate. Findings compatible with foreign body type granuloma caused by polymethylmethacrylate (hematoxylin-Eosin; x4).



the history of PMMA application coincided with an abrupt and severe manifestation of clinical symptoms related to rheumatoid arthritis.

DISCUSSION

Rhinoplasty remains an established technique for aesthetic improvement of the nose. Like all surgical procedures, it has a considerable period of recovery and downtime from activities of daily living, poses risks, and a possible need for surgical revision. In this context, the use of non-surgical filling agents seeking to improve nasal shape and aesthetics has found more and more interest. An almost immediate result, no need for hospitalization, lower cost, and apparent simplicity of the method, may argue for this approach.[13] Ideally, injectable fillers should be biocompatible, safe, stable in the place where they are applied, without the ability to migrate, and should not induce the formation of foreign body granulomas. PMMA was, for a long time, considered a material that is widely available, safe, easy to apply, and has few unwanted effects. Thus, it was recommended for use in various body regions, including the face and nose.[14] Like any filler, despite good and long-lasting results in many patients, complications started to become evident with the use of this alloplastic material. PMMA is a synthetic and permanent filler polymer. It is composed of tiny spherical particles suspended in different vehicles such as hyaluronic acid, ascorbic acid, or even animal collagen. AEs with this product can be immediate, early or late. The most frequent adverse events are nodule formation, inflammation, discoloration, and allergic reactions.[15] Nodules, inflammatory reactions, and infections may be related to the formation of a bacterial biofilm.[16,17] The immediate AEs are fundamentally related to accidental intravascular injection, producing embolization and tissue damage of variable intensity.[18] Sometimes they can lead to tissue necrosis, visual damage or blindness.[19,20] The early adverse effects are edema, erythema, pain, itching, inflammation, or infection. Deformities can occur due to technical error or the use of an inadequate amount of material. Late complications can develop many months or years after the application of this type of filler. Foreign body granuloma is the

most common of these adverse events. This diagnosis warrants histologic analysis.[21] In the nose, these granulomas can lead to discomfort, asymmetries, ulceration, aesthetic impairment, neovascularization, inflammatory processes, recurrent edema, and functional impairment.

The clinical incidence of granulomatous reaction by filling materials in the face appears to be low and related to the characteristics of the product, its structure and quality. Uniform size and shape of the particles and an adequate application technique contribute to a lower risk of granuloma formation. The presence of PMMA in soft tissues such as the nose can induce the formation of a foreign body reaction with deposits of fibrotic tissue. The incidence of AEs in the face, including granulomas with the use of PMMA, is estimated as 3%. Granulomas usually appear between 6 and 24 months after application with an incidence of 0.6 %. However, it is not uncommon that they appear much later after the injection.[22]

The unique structure of the nose, characterized by the scarcity of subcutaneous tissue and the intimacy of the skin with cartilage, bone and mucosa, may be related to the appearance of these AEs. Histologic evaluation of granulomas resulting from PMMA demonstrates nodular or diffuse granulomatous infiltrates; small particles of the material, generally rounded, translucent and of homogeneous size; in addition to multinucleated giant cells (Figure 11). These foreign body particles are too large to be phagocytized by macrophages. Studies suggest that late granulomas may be associated with the formation of a biofilm, a community of microorganisms encapsulated in a matrix adhering to a living or inert surface.[21]

The resources most commonly used for the treatment of complications related to PMMA are the intralesional application of triamcinolone, 5-fluorouracil, xylitol, surgical resections, and laser.[8–10,15,19] The therapeutic option will depend upon the severity, the clinical and emotional condition of the patient, the location of the deformity and functional repercussion; in addition, previous treatments may also affect the choice of current treatment. Classical surgery using closed or open rhinoplasty incisions can be performed. However, the presence of alloplastic material, fibrosis and deformities can represent a technical difficulty for surgical removal. The use of intralesional diode lasers with wavelengths of 808nm, 810nm, and 1470nm, as well as the 1064nm Nd:YAG laser have also been recommended in the management of these complications. The main objective is the heating of the polymer, creation of tunnels in the compromised tissue and fragmentation of the alloplastic filling material. The 1064nm Nd:YAG laser has a high transmission in PMMA.[10–12] During direct contact of the laser with the polymer surface, a sudden increase in temperature occurs. When the laser ceases to operate, the temperature drops below the polymer's melting point.[23] The laser energy leads to the formation of tunnels through its thermal action and photodynamic effect.[10,11] This heating of the granulomas produced by PMMA must be slow and progressive. The solid characteristic of this material argues for a high melting temperature. Thus, a higher dose of energy and greater care for skin and surrounding tissues is necessary to avoid thermal injury or carbonization of the tissue.[23]

CONCLUSION

Granulomas and deformities produced by the previous application of PMMA are often difficult to treat. Currently, there is no single effective therapeutic option for all cases. The use of the 1064nm short pulsed Nd:YAG laser, applied intralesionally, proved to be effective in this series of cases. There was an improvement in the problems related to granulomas as well as in the aesthetic deformities. Further studies are needed to determine its reproducibility and the type, characteristics, and parameters of the laser most suitable for the treatment of granulomas in the nose produced by previous injection of PMMA.

DISCLOSURES

The authors declare that they have no conflict of interest to disclose or financial relationships with industry as relevant to the topic discussed.

Funding: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior – Brazil (CAPES) – Finance Code 001.

REFERENCES

1. Wollina, Goldman. Minimally invasive aesthetic procedures in young adults. *Clin Cosmet Investig Dermatol.* Published online March 2011:19. doi:10.2147/CCID.S17467
2. Rivkin A. A prospective study of non-surgical primary rhinoplasty using a polymethylmethacrylate injectable implant. *Dermatologic Surg.* 2014;40(3):305-313. doi:10.1111/dsu.12415
3. Galadari H, Krompouzos G, Kassir M, et al. Complication of Soft Tissue Fillers: Prevention and Management Review. *J Drugs Dermatol.* 2020;19(9):829-832. doi:10.36849/JDD.2020.10.36849/JDD.2020.5084
4. Chen L, Li SR, Yu P, Wang ZX. Comparison of artecoll, restylane and silicone for augmentation rhinoplasty in 378 chinese patients. *Clin Investig Med.* 2014;37(4):203-210. doi:10.25011/cim.v37i4.21725
5. De Figueiredo JCA, Naufal RR, Zampar AG, Mélega JM. Expanded median forehead flap and abbé flap for nasal and upper lip reconstruction after complications of polymethylmethacrylate. *Aesthetic Plast Surg.* 2010;34(3):385-387. doi:10.1007/s00266-008-9294-8
6. Peled ZM, Warren AG, Johnston P, Yaremchuk MJ. The use of alloplastic materials in rhinoplasty surgery: A meta-analysis. *Plast Reconstr Surg.* 2008;121(3):85-92. doi:10.1097/01.prs.0000299386.73127.a7
7. Monreal J. Fat grafting to the nose: Personal experience with 36 patients. *Aesthetic Plast Surg.* 2011;35(5):916-922. doi:10.1007/s00266-011-9681-4
8. Limongi RM, Tao J, Borba A, et al. Complications and Management of Polymethylmethacrylate (PMMA) Injections to the Midface. *Aesthetic Surg J.* 2016;36(2):132-135. doi:10.1093/asj/sjv195
9. Urdiales-Gálvez F, Delgado NE, Figueiredo V, et al. Treatment of Soft Tissue Filler Complications: Expert Consensus Recommendations. *Aesthetic Plast Surg.* 2018;42(2):498-510. doi:10.1007/s00266-017-1063-0
10. Goldman A, Wollina U. Intralesional Neodymium YAG laser to Treat Complications of Polymethylmethacrylate. *Open Access Maced J Med Sci.* 2018;6(9):1636-1641. doi:10.3889/oamjms.2018.348
11. Goldman A, Wollina U. Polymethylmethacrylate-induced nodules of the lips: Clinical presentation and management by intralesional neodymium:YAG laser therapy. *Dermatol Ther.* 2019;32(1):e12755. doi:10.1111/dth.12755

12. Schelke LW, Decates TS, van der Lugt CIM, Pelzer L, de Mey G, Velthuis PJ. Intralesional Laser Treatment for Dermal Filler Complications. *Plast Reconstr Surg.* 2018;141(6):1361-1369. doi:10.1097/PRS.0000000000004428
13. Thomas WW, Bucky L, Friedman O. Injectables in the Nose. *Facial Plast Surg Clin North Am.* 2016;24(3):379-389. doi:10.1016/j.fsc.2016.03.014
14. Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthetic Plast Surg.* 2003;27(5):354-366; discussion 367. doi:10.1007/s00266-003-3022-1
15. Park TH, Seo SW, Kim J-K, Chang CH. Clinical Experience with polymethylmethacrylate microsphere filler complications. *Aesthetic Plast Surg.* 2012;36(2):421-426. doi:10.1007/s00266-011-9803-z
16. da Costa Miguel MC, Nonaka CFW, dos Santos JN, Germano AR, de Souza LB. Oral foreign body granuloma: unusual presentation of a rare adverse reaction to permanent injectable cosmetic filler. *Int J Oral Maxillofac Surg.* 2009;38(4):385-387. doi:10.1016/j.ijom.2009.01.013
17. Saththianathan M, Johani K, Taylor A, et al. The Role of Bacterial Biofilm in Adverse Soft-Tissue Filler Reactions. *Plast Reconstr Surg.* 2017;139(3):613-621. doi:10.1097/PRS.0000000000003067
18. Cannata-Ortiz P, Gracia C, Aouad Y, et al. Small vessel microembolization and acute glomerulonephritis following infection of aesthetic filler implants. *Diagn Pathol.* 2016;11(1):2. doi:10.1186/s13000-016-0453-y
19. Medeiros CCG, Cherubini K, Salum FG, De Figueiredo MAZ. Complications after polymethylmethacrylate (PMMA) injections in the face: A literature review. *Gerodontology.* 2014;31(4):245-250. doi:10.1111/ger.12044
20. Silva MTT, Curi AL. Blindness and total ophthalmoplegia after aesthetic polymethylmethacrylate injection: Case report. *Arq Neuropsiquiatr.* 2004;62(3 B):873-874. doi:10.1590/S0004-282X2004000500025
21. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S. Soft-Tissue Filler Complications: The Important Role of Biofilms. *Plast Reconstr Surg.* 2010;125(4):1250-1256. doi:10.1097/PRS.0b013e3181cb4620
22. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol.* 2011;64(1):1-34. doi:10.1016/j.jaad.2010.02.064
23. Schulz J. Material, process and component investigations at laser beam welding of polymers. Published online 2002.

AUTHOR CORRESPONDENCE

Alberto Goldman

E-mail:.....alberto@goldman.com.br

Vehicle Matters

The first ever tretinoin in a hydrating lotion, with a focus on comfort*

*Like all tretinoins, Altreno may cause skin irritation and dryness

Feel the difference

The formula contains a blend of glycerin, sodium hyaluronate and natural collagen to hydrate skin.

Get your free samples on **mysamplecloset.com**

Altreno®
(tretinoin) Lotion, 0.05%

INDICATIONS AND USAGE
Altreno® (tretinoin) Lotion, 0.05% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

IMPORTANT SAFETY INFORMATION
Altreno is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Skin Irritation: Patients using Altreno may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of Altreno, or discontinue use. Avoid application of Altreno to eczematous or sunburned skin.

Ultraviolet Light and Environmental Exposure: Minimize unprotected exposure to ultraviolet light, including sunlight and sunlamps. Warn patients with frequent sun exposure and those with inherent sensitivity to sunlight to exercise caution. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided.

Fish Allergies: Altreno contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

Adverse Reactions: The most common adverse reactions in clinical trials were application site dryness (4%), pain (3%), erythema (2%), irritation (1%) and exfoliation (1%).

Nursing Women: It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental health benefits of breastfeeding should be considered along with the mother's clinical need for Altreno and any potential adverse effects on the breastfed child from Altreno.

To report suspected adverse reactions, contact Customer Service at 1-800-321-4576 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

See Brief Summary of full Prescribing Information on adjacent page.

Ortho | Dermatologics™

Altreno is a trademark of Ortho Dermatologics' affiliated entities.
© 2021 Ortho Dermatologics' affiliated entities. ALT.0039.USA.21.V2.0

Find out more at AltrenoHCP.com

BRIEF SUMMARY OF PRESCRIBING INFORMATION
This Brief Summary does not include all the information needed to use ALTRENO safely and effectively. See full prescribing information for ALTRENO.

ALTRENO® (tretinoin) Lotion, for topical use
Initial U.S. Approval: 1973

INDICATIONS AND USAGE

ALTRENO® (tretinoin) Lotion, 0.05% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Skin Irritation

Patients using ALTRENO may experience application site dryness, pain, erythema, irritation, and exfoliation. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ALTRENO, or discontinue use. Avoid application of ALTRENO to eczematous or sunburned skin.

Ultraviolet Light and Environmental Exposure

Minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ALTRENO. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

Fish Allergies

ALTRENO contains soluble fish proteins. Use with caution in patients with known sensitivity or allergy to fish. Advise patients to contact their healthcare provider if they develop pruritus or urticaria.

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 2 randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied ALTRENO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (55%). Approximately 47% were Hispanic/Latino and 45% were younger than 18 years of age. Adverse reactions reported by ≥1% of subjects treated with ALTRENO and more frequently than vehicle are summarized in Table 1.

Table 1: Adverse Reactions Reported by ≥1% of Subjects Treated with ALTRENO and More Frequently than Vehicle

Adverse Reactions n (%)		
	ALTRENO N=767	**Vehicle N=783**
Application site dryness	29 (4)	1 (<1)
Application site pain[1]	25 (3)	3 (<1)
Application site erythema	12 (2)	1 (<1)
Application site irritation	7 (1)	1 (<1)
Application site exfoliation	6 (1)	3 (<1)

[1]Application site pain defined as application site stinging, burning or pain.

Skin irritation was evaluated by active assessment of erythema, scaling, hypopigmentation, hyperpigmentation, itching, burning and stinging. The percentage of subjects who were assessed to have these signs and symptoms at any post baseline visit are summarized in Table 2.

Table 2: Application Site Tolerability Reactions at Any Post Baseline Visit

	ALTRENO N=760 Mild/Mod/Severe	**Vehicle N=782 Mild/Mod/Severe**
Erythema	51%	44%
Scaling	49%	30%
Hypopigmentation	12%	10%
Hyperpigmentation	35%	35%
Itching	35%	28%
Burning	30%	14%
Stinging	21%	8%

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data on ALTRENO use in pregnant women. The systemic levels following topical administration are lower than with administration of oral tretinoin; however, absorption of this product may result in fetal exposure. There are reports of major birth defects similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoinrelated embryopathy (see Data).

Animal reproduction studies have not been conducted with ALTRENO. Topical administration of tretinoin in a different formulation to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses up to 0.5 mg tretinoin/kg/day, approximately 2 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100 times the MRHD based on BSA comparison and assuming 100% absorption) (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and 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

While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Animal Data

Tretinoin in a 0.05% gel formulation was topically administered to pregnant rats during organogenesis at doses of 0.1, 0.3 and 1 g/kg/day (0.05, 0.15, 0.5 mg tretinoin/kg/day). Possible tretinoin malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were observed at maternal doses of 0.5 mg tretinoin/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption). These findings were not observed in control animals. Other maternal and reproductive parameters in tretinoin-treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 4 g of ALTRENO applied daily to a 60-kg person.

Other topical tretinoin embryofetal development studies have generated equivocal results. There is evidence for malformations (shortened or kinked tail) after topical administration of tretinoin to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. Supernumerary ribs have been a consistent finding in rat fetuses when pregnant rats were treated topically or orally with retinoids.

Oral administration of tretinoin during organogenesis has been shown to induce malformations in rats, mice, rabbits, hamsters, and nonhuman primates. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were reported when an oral dose of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison). Increased skeletal variations were observed at all doses in this study and dose-related increases in embryo lethality and abortion were reported in this study. Similar results have also been reported in pigtail macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 10 times the MRHD based on BSA comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 4 times the MRHD based on BSA comparison.

Lactation

Risk Summary

There are no data on the presence of tretinoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ALTRENO and any potential adverse effects on the breastfed child from ALTRENO.

Pediatric Use

Safety and effectiveness of ALTRENO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to less than 17 years based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week trials and an open-label pharmacokinetic study. A total of 318 pediatric subjects aged 9 to less than 17 years received ALTRENO in the clinical studies [see Clinical Pharmacology and Clinical Studies in full Prescribing Information]. The safety and effectiveness of ALTRENO in pediatric patients below the age of 9 years have not been established.

Geriatric Use

Clinical trials of ALTRENO did not include any subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year dermal mouse carcinogenicity study was conducted with topical administration of 0.005%, 0.025% and 0.05% of a tretinoin gel formulation. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Studies in hairless albino mice with a different formulation suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect was confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes and an in vivo rat micronucleus assay. All tests were negative.

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (approximately the MRHD based on BSA comparison and assuming 100% absorption) were observed.

Distributed by:

Ortho Dermatologics, a division of Bausch Health US, LLC.
Bridgewater, NJ 08807 USA
U.S. Patent Number: 6,517,847
Altreno and Ortho Dermatologics are trademarks of Bausch Health Companies, Inc. or its affiliates.

© 2020 Bausch Health Companies Inc. or its affiliates Rev: 03/2020
ALT.0025.USA.20 9650300
Rev: 03/2020
9650300

doi:10.36849/JDD.3936

November 2021 1169 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Deoxycholic Acid (ATX-101) for Fat Reduction

Jyoti Gupta MD,[a] Martin Kassir MD,[b] George Kroumpouzos MD,[c] Andreas Katsambas MD,[d]
Hassan Galadari MD,[e] Torello Lotti MD,[f] Uwe Wollina MD,[g] Stephan Grabbe MD,[h] Mohamad Goldust MD[i]

[a]DermaClinix-The Complete Skin and Hair Solution Center, Delhi, India
[b]Worldwide laser institute, Dallas, TX
[c]Department of Dermatology, Alpert Medical School of Brown University, Providence, RI
[d]Department of Dermatology, Medical School of Jundiaí, São Paulo, Brazil;
GK Dermatology, PC, South Weymouth, MA; University of Athens, Athens, Greece
[e]College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates
[f]University of Studies Guglielmo Marconi, Rome, Italy
[g]Department of Dermatology and Allergology, Städtisches Klinikum Dresden,
Academic Teaching Hospital of the Technical University of Dresden, Germany
[h]Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
[i]Department of Dermatology, University Medical Center Mainz, Mainz, Germany

ABSTRACT

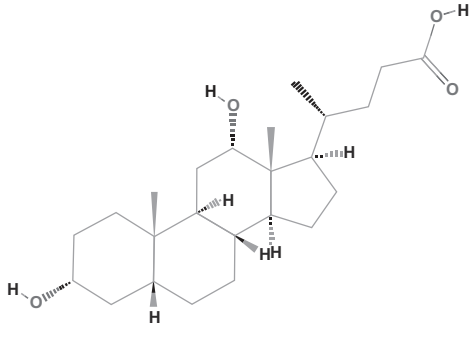
Excess, unwanted fat in submental and other body areas has been a focus of new modalities in aesthetics. Invasive and, more recently, non-invasive modalities for removal of unwanted fat have been on an increase. ATX-101 (deoxycholic acid injection) is the only injectable drug approved in the United States and Canada for reduction of moderate or severe submental fat in adults, with ongoing trials testing its efficacy in body contouring and lipomas. It has proven efficacy in submental fat reduction with a good safety profile. This article reviews the pharmacology, mechanism of action, clinical effects and adverse effects of ATX-101. It emphasizes on careful patient selection and advises on appropriate volume administration, number of treatments, and injection technique. The literature research includes peer-reviewed articles (clinical trials or scientific reviews). Studies were identified by searching electronic databases (MEDLINE and PubMed) till December 2019 and reference lists of respective articles. Only articles published in English language were included.

J Drugs Dermatol. 2021;20(11):1169-1173. doi:10.36849/JDD.3936

INTRODUCTION

Deoxycholic acid injection (DCA) is a pure synthetic formulation of deoxycholate sodium which has been patented as ATX-101.[1,2] It is one of the first injection of deoxycholate that has been FDA approved for submental fat (SMF) reduction. It is branded/marketed as Kybella® (USA), Belkyra (Canada) and ATX-101 (Allergan company, Ireland).[3,4] ATX-101 is a synthetic replicate of the in vivo bile acids (deoxycholic acid) [Figure 1], and functions as fat emulsifier.[2] Its approval for SMF reduction by the FDA and Health Canada warrants its action on fat reduction/dissolution at other sites in the future.[5]

FIGURE 1. Detailed chemical structure of deoxycholic acid



Pharmacology

ATX-101 is a synthetic replicate of endogenous DCA. The experiments on rat,[3] helped us to know that the tissue distribution of ATX-101 is similar to endogenous DCA. Even after subcutaneous injection, its secretion is mediated by liver and small bowel and is recycled by the enterohepatic circulation.[7,9]

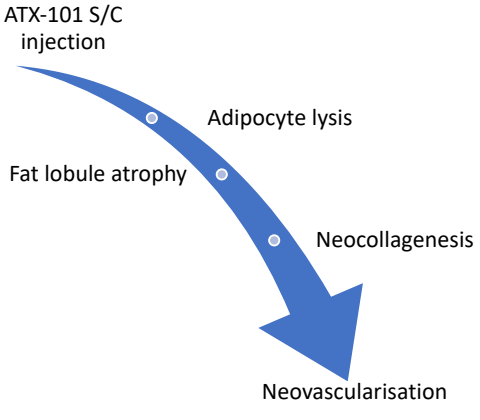
Understanding of the pharmacokinetics, pharmacodynamics, mechanism and safety profiles of ATX-101 have opened up future prospects of its uses. Walker et al[8] showed that the pharmacological profile for ATX-101 is equivalent for each treatment setting irrespective of the number of injections and the volume of administered drug. Walker et al[9] further suggested that the addition of benzyl alcohol as a preservative has no significant effects on the overall pharmacokinetic profile of ATX-101.

The administration ATX-101 has no significant effect on heart rate/routine cardiovascular system or the serum concentrations of the pro-inflammatory cytokines: interleukin 15 (IL-15), tumor necrosis factor α (TNF- α), apolipoprotein B(apo-B), adiponectin, insulin, and leptin.[10] The manufacturing of deoxycholic acid is a thoroughly devised multistep procedure. It is made sure to make it as close a biological equivalent of the in vivo bile acid. This prevents any kind of allergy or risk of animal or human related pathogens. Overall, it is a safe product with no significant alterations in lipid profile, liver function tests or kidney function tests among the patients.[11]

Mechanism of action (MoA)

The mechanism of action is derived by the structural similarity to the endogenous secondary bile acids. Thus it can be made use to dissolve the subcutaneous fat-within the submental area, abdomen, buttock- and benign adipocyte tumor (Lipoma) by a series of steps as shown in Figure 2.[1,2,]

FIGURE 2. Mechanism of action of ATX-101 subcutaneous injections.



It mediates adipocyte lysis by causing breaks in the adipocyte cell membrane which ultimately leads to cell death.[1,13] As ATX-101 destroys adipocytes and thereby stimulates the new vessels and collagen formation. Its administration results in a durable anti-ageing and fat lowering response over time.

The mechanism has been demonstrated in an open labeled study where ATX-101 was injected into the superficial abdominal fat of patients who already had plans to go for abdominoplasty.[12] Tissue samples of the fat showed histopathological changes consistent with the mechanism proposed. ATX-101 effectiveness was dose-dependent and restricted to only subcutaneous layer of the abdominal fat for all different doses evaluated with no subsequent epidermal, dermal or deep tissue changes.

Dosage and Effects

The standard dosage for ATX-101 is 1 or, more commonly, 2-mg/cm^2 and 0.2 mL volume per injection site, with injection sites spaced at 1 cm. Up to 50 injections per session can be performed depending upon surface area treated. Volume is extremely important in patients with extreme SMF as these patients may require a higher volume (ie, 10 ML ATX-101 more) to achieve their goals, as per recent clinical trial.[14] The session can be repeated after a minimum of 28 days for up to a total of 6 treatments to yield an effective SMF reduction.[15]

In the 28-day cycle of a single session, the adipocyte lysis starts on day 1 post ATX-101 injection, sequenced by neutrophilic infiltration on day 1–3 and macrophage infiltration leading to adipose tissue septa inflammation till day 7. This is followed by local tissue response and septal thickening in the next 1-2 weeks. By day 28, inflammation resolves, new blood vessels and collagen production sets in atrophy of the fat lobule, thereby dissolving the subcutaneous fat.[12]

In an effort to minimize the injection related side effects, the treatment sessions are even delayed later than 28 days to 3 months. Dover JS et al in his study showed that the tissue remodeling, and new collagen formation may continue even after 28 days of treatment.[16] Thus continuous submental fat reduction takes place for a period of 2-3 months with a single session alone. The effects of the injection keep on increasing if the sessions are given after every 28 days. In view of the findings, it is recommended that the treatment doses and dosage intervals must be maneuvered based on the individual side-effects profile of the patient.

Patient Selection

Although ATX-101 injection may reduce some amount of submental fat (SMF) in adults with moderate amount,[17] it may not be appropriate for patients with severe skin sagging of the neck. Before the injection takes place, the aesthetic provider should examine carefully the submental area to evaluate whether patient is a good candidate for SMF reduction with ATX-101. The recently published CONTOUR trial showed that patients with mild/moderate SMF at baseline were more likely to meet their goals (more defined jawline, looking younger, looking thinner) than patient with severe SMF.[14] These results are relevant to patient counseling and selection as patients with severe SMF may not be entirely pleased with outcome, and this needs to be discussed before treatment. Furthermore, patients with unrealistic expectations, e.g. getting optimal results with a single ATX-101 treatment, should be discouraged from having the treatment. All patients should be advised that they are more likely to meet their treatment goals if they undergo multiple ATX-101 treatments and receive adequate medication based on baseline SMF severity.[14]

Clinical Uses

The most prominent use of ATX is the injection into the

submental area for fat reduction. Prior to 2015, unapproved lipolytic injections with a combination of phosphatidyl-choline and sodium deoxycholate, were administered for reducing localized fat.[1,3,4] However, with the FDA approval of ATX-101, the scenario has changed. ATX-101 has been an upcoming trend because of its safe use in SMF reduction. Its efficacy and safety in reducing submental fat has been proven in many studies.[18-21] Humphrey S et al demonstrated the safety and efficacy of ATX-101 in a randomized controlled trial. They objectively measured and confirmed the submental fat reduction by magnetic resonance imaging. In their study, a significant reduction in submental fat was found among the ATX-101 treated group as compared to the placebo group. In addition, ATX-101 treated patients achieved greater satisfaction (P<0.05). Most of the side effects encountered in the study group were localized to the injection site.[22] Dayan SH pooled the data from various Phase 3 REFINE trials and found that ATX-101 injections were very effective in SMF reduction. Only 2-3 treatment sessions were enough to significantly reduce submental fat in most of the patients.[23] In addition, the results of CONTOUR trial showed that the psychological impact of SMF was reduced after ATX-101 treatment not only among patients who met their goals but also those with severe SMF who did not.[14]

Other current treatments for SMF reduction include high intensity focused ultrasound (HIFU) and surgery for platysma muscle which may be accompanied with facial liposuction of the areas of chin. The last two treatments are mildly invasive in nature, and studies confirming the clinical effects of HIFU are pending.[24]

Off-Label Uses

Although FDA approval for ATX-101 is limited only to SMF, its effectiveness to reduce fat in other areas are under clinical trials: NCT00608842 and NCT00422188 for superficial lipomas and NCT00835952 for reduction of abdominal fat in abdominoplasty candidates; whose results are still awaited.[25] Its use in benign fat tumors may not yield immediate success just for the fact that the pathology of these tumors is more complex than excess fat. They may show varied histopathology and subtypes, eg, lipomatous lipoma, fibrolipoma, angiolipoma, myxolipoma, myolipoma, spindle cell lipoma, and chondrolipoma. As ATX-101 is only a lipolytic agent, other components in lipoma, eg, blood vessels, muscles, and fibrous tissue, may not be effectively dissolved. Thus, there are chances of persistence and recurrence of lipomas.

Deoxycholic acid, the active component of ATX-101, can be used to dissolve subcutaneous fat in any body area. Its use in body contouring was adjudged by Shridharani SM and Chandawarkar AA.[26] This effort was made by Shridharani SM after finding good results for neck contouring on 100 consecutive patients with the use of ATX-101 injections.[27] In the study on body contouring, the authors injected 14 patients with 0.2 mL of deoxycholic acid injection (10 mg/mL concentration, dose 2 mg/cm2) at various specific regions identified as target areas for fat reduction. A total of 3 treatments were performed, and results were favorable (100% improvement in contouring) in peri-axillary area, inner and outer thighs, upper arms, knees and jowls. The treatment was without any significant adverse effects like skin necrosis, skin pigmentation, abnormal contouring, abnormal vascular response, or abnormal sensory or motor dysfunction; during the follow up till 10 weeks. The main study limitation was the small number of patients that were enrolled in the study (n=14); which limits the validity of ATX-101 use in body contouring. In one of the latest single case reports, ATX-101 has been found effective in dissolving paradoxical adipose hyperplasia in the abdomen after cryolipolysis.[28] Such findings encourage the use of ATX-101 in dissolving fat in other body areas as well.

Based on the results we recommend further large studies of ATX-101 on patients of body contouring with a regular long follow-up to monitor the response and the side effects. The success of future studies may help in introducing ATX-101 as a standard alternate therapy to reduce fat in body areas in a non-invasive manner.

Side Effects Profile

ATX-101 injections are minimally invasive and overall, well tolerated. They may cause transient adverse effects (AEs), with permanent adverse effects such as atrophic or hypertrophic scarring, being uncommon.[29,30,31] Almost all patients who are injected with ATX-101 experience injection site local AEs like pricking, discomfort, edema, oozing of blood in the skin, sensory disturbance: numbness or paresthesia, redness, thickness and formation of lump/nodule - owing to the subcutaneous mode of injection and mechanistic action of ATX-101. Such AEs may not require any active intervention and resolve by itself within 4 weeks. The AEs also show the property of adaptation: the intensity and severity decreases with every subsequent treatment session. However, one may use ice packs or local anesthesia before the injection to mitigate the pain and discomfort of the injection.[15]

Adverse effects related to faulted injection technique include nerve paresis, and skin ulceration. Dysphagia may occur due to the increased volume of injection. The detailed list of AE with ATX-101 has been shown in Table 1.[32]

Tips for Injecting ATX-101

Familiarity with anatomy and proper injection technique are of paramount importance. Any fault in the injection technique or inadequate knowledge of the anatomical site being treated may cause nerve injury and skin ulceration.[33] After cleansing the area to be treated with a topical antiseptic, the injector should mark the outline area with a surgical pen. In addition,

TABLE 1.

Reported AEs of ATX-101	
Location	**Adverse Effect**
Injection site	Alopecia
	Bleeding
	Dysphagia
	Edema
	Erythema
	Hematoma
	Hyperhidrosis
	Induration
	Injury of mandibular nerve branch
	Nodule
	Numbness
	Pain
	Pallor
	Paraesthesia
	Pruritus
	Tightness
	Warmth
	Atrophic scarring
	Hypertrophic scarring
Noninjection site	Headache
	Nasopharyngitis
	Tremor

a "no treatment" zone is marked around the probable location of the marginal mandibular nerve.[34] Then an injection grid with spacing between injection sites 1 cm is applied to the treatment area to control injection spacing. The injections (0.2 mL per injection site) should be performed with a 30-G 0.5-inch needle at an appropriate depth (midpoint into the preplatysmal submental fat), as superficial injections may result in skin ulceration.[34] A maximum volume of 10 mL is administered per treatment session.[34] Injection may cause local pain, thus application of cold packs or local anesthetic (topically applied or injectable) is recommended to comfort the patient. A proper technique is important, and adequate training is warranted for optimal outcome with minimal side effects. Recurrence is usually prevented due to the subdermal, but any weight gain may cause the fat to deposit around the treated area.[15]

A proper injection site should avoid the inferior mandibular border, therefore, ATX should not be injected above a line drawn 1–1.5 cm below the inferior border of the mandible.[3,34] In addition, one should examine and palpate the submentum and feel the muscle and the fat; to make sure the injection goes in the preplatysmal fat (half way into it), avoiding injury to platysma or dermis.[5] Finally, some of the co-authors and other aesthetic providers mix ATX-101 with a few units of hyaluronidase prior to injection to enhance a more even and better spread of ATX-101 in the tissue (anecdotal).

Pain and discomfort with ATX-101 injection can be troublesome for some patients. The manufacturer recommends the use of ice packs to numb the area for decreasing the pain. Some patients also experience burning sensation just after the injection. Rauso showed that ATX-101 premixed with lidocaine 2% helps decrease pain/discomfort and reduces the requirement of post injection analgesic drugs without interfering with the effectiveness for SMF reduction therapy.[35] In another study, Sherman[36] demonstrated that the patient pain/discomfort could be reduced by keeping the injection loaded and ready to inject to complete the procedure as quickly as possible. Fagien S et al completed a Phase 3b trial on the adverse effects of ATX-101 injection and recommended the use of oral non-steroidal anti-inflammatory drugs such as ibuprofen and/or acetaminophen (one hour before) and lidocaine (15 minutes) before the treatment, and cold application after the treatment. [37] They also cautioned against the continuation of any drug that may interfere with coagulation. The manufacturer suggests applying local anesthesia for pain reduction and waiting for 15–20 minutes between local anesthesia administration and ATX-101 injection. This is suggested to avoid any reduction in the efficacy of the ATX-101 injection, which may be caused by local swelling in the area or the dilution of ATX-101 injection due to local anesthesia injection.[35]

CONCLUSION

ATX-101 provides a safe and effective approach to superficial fat dissolution with confirmed approval for SMF and ongoing research for other body parts. The understanding of its mechanism as a whole holds the key in enabling its use in aesthetics. The mild adverse effects of this modality usually resolve spontaneously, thus requiring no active intervention. The use of ATX-101 in non-submental areas is promising, but more studies are required to evaluate its efficacy and longevity of correction.

DISCLOSURES

Uwe Wollina had been taken part in a phase III trial for ATX-101.

REFERENCES

1. Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg.* 2004;30:1001–1008.
2. Stryer L. Biosynthesis of membrane lipids and steroids. In: Biochemistry (Fourth Edition). New York (NY): WH Freeman & Company; 1995. p. 691–707.
3. Kythera Biopharmaceuticals, Inc. KybellaTM (deoxycholic acid) injection [prescribing information]. 2015 [cited 2015 Oct 26]. Available from: http://www.mykybella.com/Content/Documents/KYBELLA-Combined-FINAL-Labeling.pdf.
4. US Food and Drug Administration. FDA issues warning letters for drugs

promoted in fat elimination procedure. 2010 [cited 2015 Oct 26]. Available from: http://www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm207453.htm.
5. Ascher B, Fellmann J, Monheit G. ATX-101 (deoxycholic acid injection) for reduction of submental fat. Expert Rev Clin Pharmacol. 2016;9(9):1131-43.
6. Angelin B, Björkhem I, Einarsson K. Individual serum bile acid concentrations in normo- and hyperlipoproteinemia as determined by mass fragmentography: relation to bile acid pool size. *J Lipid Res.* 1978;19:527–537.
7. Dawson PA. Bile secretion and the enterohepatic circulation of bile acids. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. Philadelphia (PA): Saunders; 2002. p. 1051–1064.
8. Walker P, Havlickova B, Lee D. ATX-101 for reduction of submental fat: pharmacokinetic and safety findings from a phase I trial [abstract]. Presented at: 8th European Masters in Aesthetic and Anti-Ageing Medicine; 2012 Oct 12–14; Paris, France.
9. Walker P, Fellmann J, Lizzul PF. A phase I safety and pharmacokinetic study of ATX-101: injectable, synthetic deoxycholic acid for submental contouring. *J Drugs Dermatol.* 2015;14:279–287.
10. Walker P, Lee D. A phase 1 pharmacokinetic study of ATX-101: serum lipids and adipokines following synthetic deoxycholic acid injections. *J Cosmet Dermatol.* 2015;14:33–39.
11. Dayan SH, Humphrey S, Jones DH, Lizzul PF, Gross TM, Stauffer K, et al. Overview of ATX-101 (deoxycholic acid injection): a nonsurgical approach for reduction of submental fat. *Dermatol Surg.* 2016;42 Suppl 1:S263-S270.
12. Walker P, Lee D, Toth BA. A histological analysis of the effects of single doses of ATX-101 on subcutaneous fat: results from a phase 1 open-label safety study of ATX-101 [abstract]. Presented at: 1st Anti-aging Medicine European Congress; 2013 Oct 11–12; Paris, France.
13. Thuangtong R, Bentow JJ, Knopp K, Mahmood NA, David NE, Kolodney MS. Tissue-selective effects of injected deoxycholate. *Dermatol Surg.* 2010;36:899–908.
14. Behr K, Kavali CM, Munavalli G, Teller CF, Yoelin S, Breshears L, et al. ATX-101 (deoxycholic acid injection) leads to clinically meaningful improvement in submental fat: final data from CONTOUR. *Dermatol Surg.* 2019;00:1-8.
15. Dunican KC, Patel DK. Deoxycholic acid (ATX-101) for reduction of submental fat. *Ann Pharmacother.* 2016;50(10):855-61.
16. Dover JS, Shridharani SM, Bloom JD, Somogyi C, Gallagher CJ. reduction of submental fat continues beyond 28 days after ATX-101 treatment: results from a post hoc analysis. *Dermatol Surg.* 2018;44(11):1477-1479.
17. Kybella PI, ed. Kybella (Deoxycholic Acid) Injection Prescribing Information. Westlake Village, CA: Kythera Biopharmaceuticals, Inc; 2015.
18. Ascher B, Hoffmann K, Walker P, Lippert S, Wollina U, Havlickova B. Efficacy, patient-reported outcomes and safety profile of ATX-101 (deoxycholic acid), an injectable drug for the reduction of unwanted submental fat: results from a phase III, randomized, placebo-controlled study. J *Eur Acad Dermatol Venereol.* 2014;28(12):1707-15.
19. Jones DH, Carruthers J, Joseph JH, Callender VD, Walker P, Lee DR, et al. REFINE-1, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial with ATX-101, an injectable drug for submental fat reduction. *Dermatol Surg.* 2016;42(1):38-49.
20. Rzany B, Griffiths T, Walker P, Lippert S, McDiarmid J, Havlickova B. Reduction of unwanted submental fat with ATX-101 (deoxycholic acid), an adipocytolytic injectable treatment: results from a phase III, randomized, placebo-controlled study. *Br J Dermatol.* 2014;170(2):445-53.
21. McDiarmid J, Ruiz JB, Lee D, Lippert S, Hartisch C, Havlickova B. Results from a pooled analysis of two European, randomized, placebo-controlled, phase 3 studies of ATX-101 for the pharmacologic reduction of excess submental fat. *Aesthetic Plast Surg.* 2014;38(5):849-60.
22. Humphrey S, Sykes J, Kantor J, Bertucci V, Walker P, Lee DR, et al. ATX-101 for reduction of submental fat: A phase III randomized controlled trial. *J Am Acad Dermatol.* 2016;75(4):788-797.e7.
23. Dayan SH, Schlessinger J, Beer K, Donofrio LM, Jones DH, Humphrey S, et al. Efficacy and safety of ATX-101 by treatment session: pooled analysis of data from the phase 3 REFINE trials. *Aesthet Surg J.* 2018;38(9):998-1010.
24. Wollina U, Goldman A. ATX-101 for reduction of submental fat. *Expert Opin Pharmacother.* 2015;16:755-762.
25. ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed May 5, 2016.
26. Shridharani SM, Chandawarkar AA. Abstract. Plastic and Reconstructive Surgery - Global Open. 2017;5:53.
27. Shridharani SM. Early experience in 100 consecutive patients with injection adipocytolysis for neck contouring with ATX-101 (Deoxycholic Acid). *Dermatol Surg. 2*017;43(7):950-958.
28. Ward CE, Li JY, Friedman PM. ATX-101 (Deoxycholic Acid Injection) for Paradoxical Adipose Hyperplasia Secondary to Cryolipolysis. *Dermatol Surg.* 2018;44(5):752-754.
29. Goodman G, Smith K, Walker P, Lee D. Reduction of submental fat with ATX-101: a pooled analysis of two international multicenter, double-blind, randomized, placebo-controlled studies. J Am Acad Dermatol. 2012;66:AB23.
30. Walker P, Fellmann J, Lizzul PF. A phase I safety and pharmacokinetic study of ATX-101: injectable, synthetic deoxycholic acid for submental contouring. *J Drugs Dermatol.* 2015;14:279–287.
31. Ramirez MR, Marinaro RE, Warthan ML, Burton CS. Permanent Cutaneous Adverse Events After Injection With Deoxycholic Acid. *Dermatol Surg.* 2019;45(11):1432-1434.
32. Souyoul S, Gioe O, Emerson A, Hooper DO. Alopecia after injection of ATX-101 for reduction of submental fat. *JAAD Case Rep.* 2017;3(3):250-252.
33. Woltmann M, Faveri R, Sgrott EA. Anatomosurgical study of the marginal mandibular branch of the facial nerve for submandibular surgical approach. *Braz Dent J.* 2006;17:71–74.
34. Jones DH, Kenkel JM, Fagien S, Glaser DA, Monheit GD, Stauffer K, et al. Proper Technique for Administration of ATX-101 (Deoxycholic Acid Injection): Insights From an Injection Practicum and Roundtable Discussion. *Dermatol Surg.* 2016;42 Suppl 1:S275-S281
35. Rauso R. Deoxycholate (ATX-101) Mixed with Lidocaine to Minimize Pain/Discomfort in Nonsurgical Treatment of Submental Fullness Appearance. *J Cutan Aesthet Surg.* 2018;11(4):229–233.
36. Sherman D. Practical and theoretical course. Rome, Italy: 2017. Ri-definire il profilo.
37. Fagien S, McChesney P, Subramanian M, Jones DH. Prevention and Management of
38. Injection-Related Adverse Effects in Facial Aesthetics: Considerations for ATX-101 (Deoxycholic Acid Injection) Treatment. *Dermatol Surg.* 2016;42 Suppl 1:S300-S304.

AUTHOR CORRESPONDENCE

Mohamad Goldust MD

E-mail:..... mgoldust@uni-mainz.de

doi:10.36849/JDD.6182

November 2021 1174 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Single-Center, Prospective, Double-Blind, Evaluator-Blind, non-Randomized, Vehicle-Controlled Trial With a 1927 nm Non-Ablative Fractionated Laser and Topical 0.05% Tretinoin Lotion for Facial Dyspigmentation and Photodamage

Rawaa Almukhtar MD MPH, Emily Carr MD, Kunal Angra MD, Michael Lipp DO, Monica Boen MD, Mitchel P. Goldman MD

Cosmetic Laser Dermatology: A West Dermatology Company, San Diego, CA

ABSTRACT

Background: Dyspigmentation and photodamage are common concerns in patients who seek aesthetic consultation. A number of treatment modalities have been utilized to address this issue. 1927 nm thulium fiber laser is a fractionated non-ablative laser that has been shown to be safe and effective in treatment of photoaging. Topical retinoids have been used for over two decades for photoaging to promote epidermal hyperplasia and collagen synthesis and to decrease melanin production. There has been lack of data to support the combination of topical retinoids with laser treatments in the management of facial dyspigmentation and photodamage.

Objective: The primary objective of this study is to evaluate the benefits and subject satisfaction resulting from use of a 1927 nm thulium fiber laser with and without 0.05% tretinoin lotion for facial dyspigmentation and photodamage.

Results: Both groups showed a significant change in Investigator Assessed Overall Hyperpigmentation and Investigator Assessed Overall Photodamage over time ($P<0.001$). No statistically significant differences were seen between groups at any time point as measured by investigator reported and subject reported efficacy scales except for Subject Global Aesthetic Improvement Scale and Subject Satisfaction at 30 days after laser treatment, at which patients who received 0.05% tretinoin lotion reported a lower level of improvement (2.8 ± 0.86 in the treatment group vs 2 ± 0.85 in the vehicle group, $P=0.009$) and lower patient satisfaction when compared to the vehicle group (2.87 ± 1.55 in the treatment groups vs 1.53 ± 0.64 in the vehicle group, $P=0.001$).

Conclusion: In our study, patients tolerated the combination of 1927 nm thulium fiber laser and 0.05% tretinoin lotion well. Both groups resulted in significant reduction of hyperpigmentation and photodamage. Subject satisfaction and perceived improvement were temporarily lower at 30 days only when, combining 0.05% tretinoin lotion with 1927 nm thulium fiber laser. Future studies are needed to investigate the impact on efficacy when combining laser procedures with a longer duration of use or a higher concentration of topical tretinoin.

J Drugs Dermatol. 2021;20(11):1174-1179. doi:10.36849/JDD.6182

INTRODUCTION

Dyspigmentation and photodamage are common concerns in patients who seek aesthetic dermatologic consultation. Intrinsic aging and cumulative sun exposure, along with other extrinsic factors such as pollution and smoking, lead to decreased collagen synthesis, increased matrix metalloproteases (MMP), and increased melanin production.[1] There are several techniques for diminishing the signs of photodamage ranging from topical anti-aging cosmeceuticals to laser and energy based- therapies.

Given its safety, efficacy, and limited downtime, fractionated non-ablative resurfacing has become a mainstay treatment for photoaging. The 1927 nm thulium fiber laser (TFL) is a fractionated non-ablative laser that induces superficial epidermal resurfacing to a maximum depth of 300 µm.[2] TFL has a relatively high absorption coefficient for water leading to its ability to target epidermal process such as dyschromia and signs of photodamage. Furthermore, the TFL produces columns of thermal necrosis in the superficial skin layers. This leads to collagen stimulation in the dermis and clearance of epidermal pigment.[3]

Topical retinoids such as tretinoin have been used for over two decades for photoaging to promote epidermal hyperplasia, MMP inhibition, collagen synthesis, and dispersion of melanin granules.[4] A novel 0.05% tretinoin lotion was recently introduced for the treatment of moderate to severe acne.[5] This novel 0.05% tretinoin lotion was formulated using polymeric emulsion technology, with the specific aim of providing more efficient delivery of retinoid into the dermal layers with less skin irritation and higher tolerability profile.[6]

In this study we examined the effects of a regimen of a topical 0.05% tretinoin lotion vs vehicle applied before and after fractionated non-ablative 1927 laser treatment.

MATERIALS AND METHODS

This was a single-center, prospective, non-randomized, double blind, vehicle -controlled, institutional review board (IRB)-approved clinical trial that was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization.

After obtaining informed consent, 41 subjects Fitzpatrick skin type I-V over the age of 18 with moderate facial hyperpigmentation and photodamage on the investigator overall hyperpigmentation and photodamage scales (Table 1) were enrolled. Subjects were excluded if they were pregnant or breastfeeding; had ablative laser resurfacing in the treatment area within the previous 6 months; had non-ablative laser in the treatment area within the previous 3 months; used topical tretinoin, adapalene, tazarotene, hydroquinone, imiquimod, 5-fluorouracil, ingenol mebutate, concentrated hydrogen peroxide, or diclofenac on the treatment area within the previous 1 month; using oral treatment with any photosensitizing drugs (doxycycline, tetracycline, isotretinoin, sulfonylureas, sulfonamides); had a facial peel or microdermabrasion of the treatment area within the previous 1 month; had known allergies or sensitivities to any of the ingredients of any topical products being used in this study; or had any pre-existing dermatological condition in the treatment area.

Intervention

21 subjects were randomized to receive the topical 0.05% tretinoin lotion (Altreno, Ortho Dermatologics, Skillman, NJ) and 20 subjects were randomized to receive a vehicle. Both groups underwent one session of 1927 nm TFL (Fraxel Dual; Solta, Hayward CA). First, the face was cleansed with alcohol, and a thin layer of compounded 23% lidocaine and 7% tetracaine was applied for 60 minutes. Prior to treatment, the anesthetic was fully wiped off and then face was cleaned again with rubbing alcohol to ensure face was free of all moisture and water. Full face was treated with 1927 nm TFL with a fluence of 20 mJ, treatment level of 5–7 (in skin types I–IV) and treatment level 3–5 (in skin types V), and total of 8 passes. Triamcinolone 0.1% ointment (Perrigo, Melville, NY) was applied to the entire face immediately after treatment. All patients followed the post-procedure instructions on days 1–7. 3D digital photography using the Canfield Vectra 3-dimensional imaging system (Canfield Scientific in Parsippany, New Jersey) was obtained at baseline, 8 days, 30 days, 90-day, and 180-day follow up.

TABLE 1.

Patient Demographics		
	Treatment (Altreno)	Vehicle
Mean Age (StDev)	55.7 (10.9)	55.4 (9.6)
Sex	21 Female/ 0 Male	20 Female/ 0 Male
Fitzpatrick Type		
I	0	1
II	5	5
III	12	9
VI	4	4
V	0	1
Mean Baseline Overall Photodamage Score (StDev)	7.23 (1.83)	6.81 (1.60)
Mean Baseline Overall Hyperpigmentation Score (StDev)	5.78 (1.89)	5.35 (1.46)

Subjects started the 0.05% tretinoin lotion or the vehicle 1 month prior to the 1927 nm TFL treatment. The 0.05% tretinoin lotion and the vehicle were held for 2 days before and 7 days after laser treatment and then restarted on day 8 for the remainder of the course of the study. All subjects were instructed to use a gentle face cleanser and a sunscreen containing zinc oxide with SPF 50. Clinical efficacy was assessed using investigator overall hyperpigmentation scale (0=none, 1–3=mild, 4–6=moderate, 7–9=severe), investigator overall photodamage scale (0=none, 1–3=mild, 4–6=moderate, 7–9=severe), Investigator Global Aesthetic Improvement Score (IGAIS) (1=much improved, 2=improves, 3=no change, 4=worse, 5=much worse), and Investigator Percent Improvement Evaluation. Subject-reported efficacy outcomes included Subject Global Aesthetic Improvement Scale (SGAIS) (1=much improved, 2=improves, 3=no change, 4=worse, 5=much worse), Subject Satisfaction (1=extremely satisfied, 2=satisfied, 3=slightly satisfied, 4=slightly dissatisfied, 5=dissatisfied, 6=extremely dissatisfied) and Patient Self-Assessment Questionnaire. Investigator overall hyperpigmentation and photodamage assessments, IGAIS, SGAIS, and Subject Satisfaction assessment were performed at the time of laser treatment and at 8-day, 30-day, 90-day, and 180-day follow up; patient self-assessment questionnaire was completed at 180-day follow up.

Statistical Analyses

All statistical tests were two-sided and interpreted at a 5% significance level. Descriptive statistics (ie, mean, standard deviation, etc) were provided for all continuous variables, frequencies for all categorical variables. In order to track changes for individual variables across all relevant visits, single-factor Analysis of Variance (ANOVA) tests was used, while comparisons between two individual visits were done using two-sample t-tests assuming equal variance. *P*-values <0.05 will be considered clinically significant.

RESULTS

Out of the 41 patients enrolled in the trial, three patients were lost to follow up (2 active patients and 1 vehicle patient). 19 patients received tretinoin 0.05% lotion and 19 patients received the vehicle prior to treatment. All subjects were females; the mean age was 55.7 ± 10.9 in the treatment group and 55.4 ± 9.6 in the vehicle group (Table 1).

Both groups showed a significant change in Investigator Assessed Overall Hyperpigmentation and Investigator Assessed Overall Photodamage over time ($P< 0.001$, Both, Single Factor ANOVA), no statistically significant differences were seen between groups at any time point (Figures 1 and 2).

FIGURE 1. Mean Investigator Assessed Overall Hyperpigmentation scores comparing 30 days prior to the laser procedure, baseline, day 8, day 30, day 90, and day 180. While both groups showed a significant change in Investigator Assessed Overall Hyperpigmentation over time ($P<0.001$), no statistically significant differences were seen between groups at any time point.

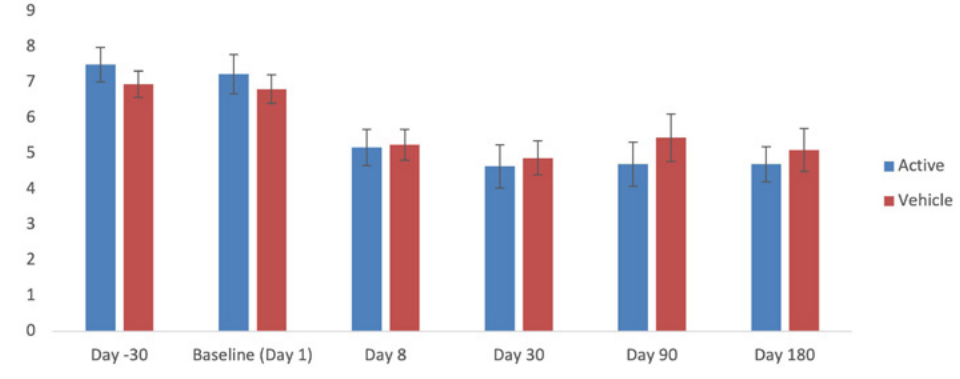


FIGURE 2. Mean Investigator Assessed Overall Photodamage scores comparing 30 days prior to the laser procedure, baseline, day 8, day 30, day 90, and day 180. While both groups showed a significant change in Investigator Assessed Overall Photodamage over time ($P<0.001$), no statistically significant differences were seen between groups at any time point.

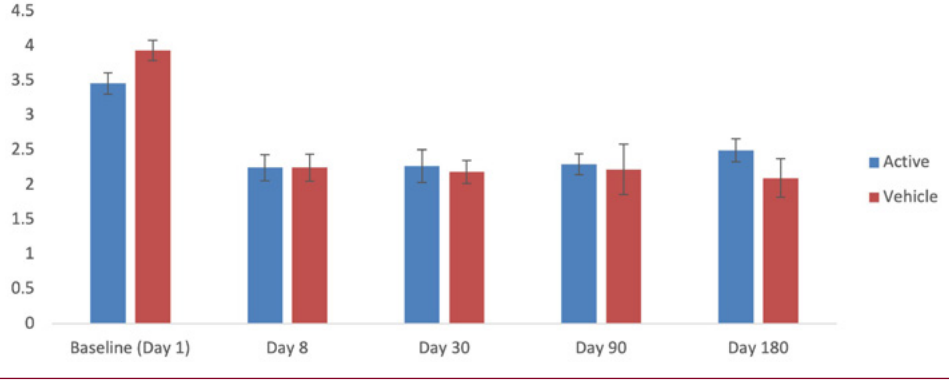
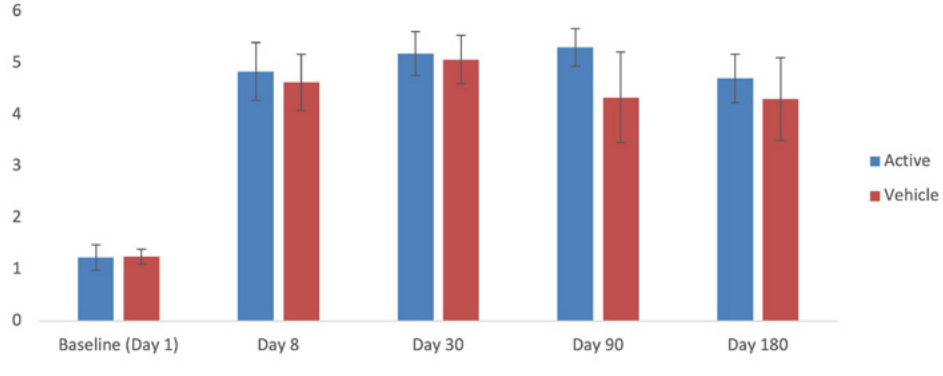


FIGURE 3. Mean Investigator Global Aesthetic Improvement (IGAIS) comparing baseline, day 8, day 30, day 90, and day 180.



No statistically significant difference in the IGAIS (Figure 3) or the Investigator Percent Improvement Score (Figure 4) was seen between groups at any time point. IGAIS at day 90 and 180 were 2.3±0.48 and 2.5±0.52 for the active group, respectively. IGAIS at day 90 and day 180 were 2.22±1.09 and 2.1±0.88 for the vehicle group, respectively.

Subjects in the active group scored significantly lower on the SGAIS than those in the vehicle group on day 30, higher scores correlate with lower level of improvement (*P*=0.009; Figure 5). Mean SGAIS of those in the active group were 3.4 ± 1.06, 2.27± 0.88, 2.8 ± 0.86, 2.79± 0.89, 3.07 ± 0.62 at baseline, day 8, day 30, day 90, and day 180, respectively. SGAIS scores for vehicle

FIGURE 4. Mean Investigator Percent Improvement Evaluation comparing baseline, day 8, day 30, day 90, and day 180.

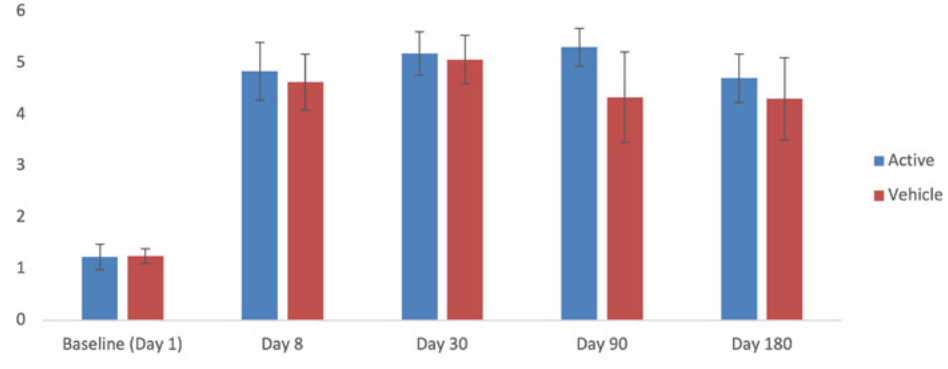


FIGURE 5. Mean Subject Global Aesthetic Improvement Scale (SGAIS) Evaluation comparing baseline, day 8, day 30, day 90, and day 180. at day 30, subjects in the Active group scored significantly higher on the SGAIS than those in the Vehicle group (*P*=0.009).

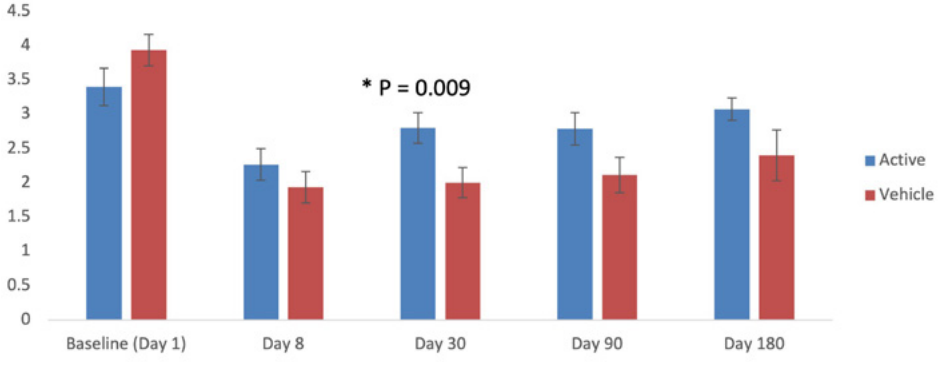


FIGURE 6. Mean Subject Satisfaction comparing baseline, day 8, day 30, day 90, and day 180. At day 30, subjects in the Active group scored significantly higher on the Subject Satisfaction Scale than those in the Vehicle group (*P*=0.001).

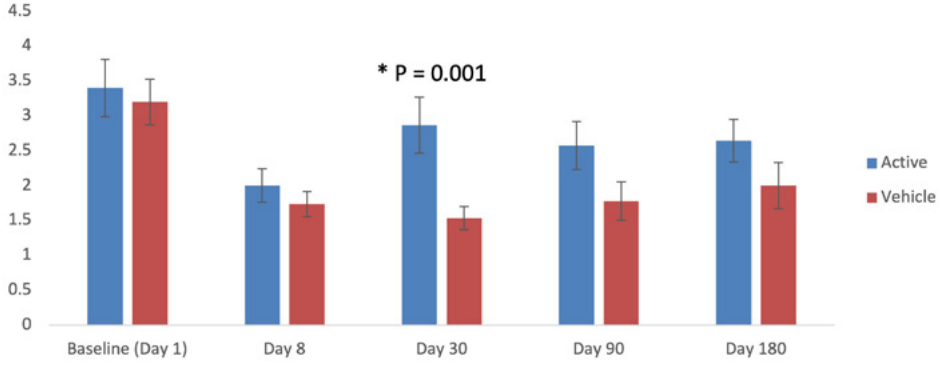
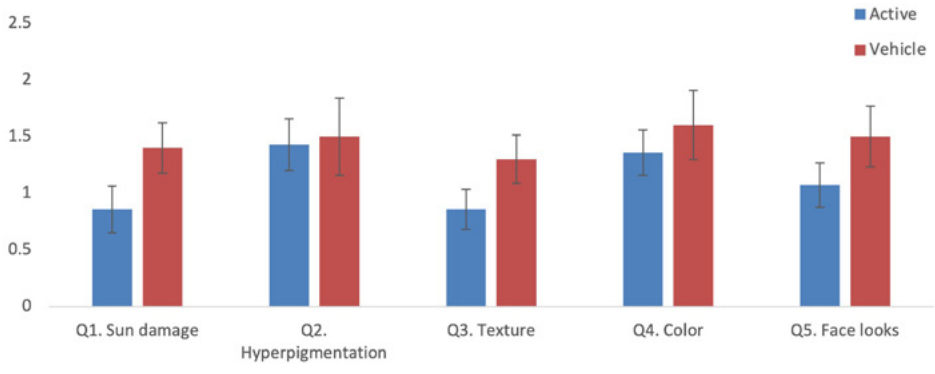


FIGURE 7. Mean Patient Self-Assessment Questionnaire at day 180. No statistically significant difference was observed between groups in response to any Patient Self-Assessment question.



group were 3.93±0.88, 1.93±0.88, 2±0.85, 2.11±0.78, 2.4±1.17, at baseline, day 8, day 30, day 90, and day 180.

Subjects in the active group scored significantly lower on the Subject Satisfaction Scale than those in the Vehicle group on day 30, higher scores correlate with lower level of satisfaction (*P*=0.001; Figure 6). Mean Subject Satisfaction Scale scores for those in the active group were 3.4±1.59, 2±0.93, 2.87±1.55, 2.57±1.28, 2.64± 1.15 at baseline, day 8, day 30, day 90, and day 180, respectively. Mean Subject Satisfaction Scale scores for those in the vehicle group were 3.2±1.26, 1.73±0.70, 1.53±0.64, 1.78±0.83, 2± 1.05 at baseline, day 8, day 30, day 90, and day 180, respectively.

No statistically significant difference was observed between groups in response to any Patient Self-Assessment question (sun damage, hyperpigmentation, texture, color, and youthful appearance of face; Figure7). Adverse events were few. One patient in the active treatment group developed acne following the treatment which can occur following fractional non ablative lasers.

DISCUSSION

Topical tretinoin is sometimes advocated to be used by clinicians in combination with a number of cosmetic procedures including dermabrasion, chemical peels, and laser treatments. Such recommendations stem from the effects of topical tretinoin on

FIGURE 8. Subject in the active group at day 1, day 8, day 30, day 90, day 180. Improvement is seen in in hyperpigmentation and photodamage between day 1 and day 180, a-frontal view, b- right side, c- left side.

FIGURE 9. Subject in the vehicle group at day 1, day 8, day 30, day 90, and day 180. Improvement is seen in photodamage and hyperpigmentation between day 1 and day 180, a-frontal view, b- right side, c- left side.

collagen production and its role in MMP inhibition and from data related to the use of tretinoin in combination with chemical peels or dermabrasion.[7,8] However, clinical studies have been sparse on the benefits of combining tretinoin with laser/ intense pulsed light (IPL) procedures.[9-11]

In this single-center, prospective, double-blind evaluator-blind, non-randomized, vehicle-controlled trial, subjects underwent one treatment with a 1927 nm TFL following pre-treatment with 0.05% tretinoin lotion or vehicle 30 days prior to the laser treatment. The topical tretinoin and the vehicle were held 2 days before and 7 days after laser treatment and were resumed at day 8 after the laser treatment and were continued until the end of the study.

Although most clinical endpoints did not show a statistically significant difference between the groups, both SGAIS (mean of 1.5 ± 0.6 in the vehicle group vs 2.9 ± 1.5 in the 0.05% tretinoin lotion group) and subject satisfaction scores (mean of 2 ± 0.9 in the vehicle group vs 2.8 ± 0.9 in the 0.05% tretinoin lotion group) were temporarily lower in the topical 0.05% tretinoin lotion when compared to the vehicle group at 30 days after the laser procedure. The combination of a topical 0.05% tretinoin lotion with fractionated non-ablative laser was well-tolerated by subjects and there were no significant adverse effects reported. One possible explanation for the lower patient reported improvement and satisfaction scores at 30 days only is due to irritation from the tretinoin lotion. This is consistent with reported transient increase in mean scores for scaling, burning, and stinging when the same 0.05% tretinoin lotion was used at 4 weeks.[5]

Our results are similar to Orringer et al, who demonstrated no significant difference in biochemical markers assessing collagen formation or in clinical end points in patient pre-treated with 0.05% tretinoin cream 21 days prior to carbon dioxide laser resurfacing.[10] Furthermore, a study by West et al revealed no significant decrease in rates of post-CO2 laser resurfacing hyperpigmentation with the pre-operative use of tretinoin for at least 2 weeks.[11] These results can be attributed in part to the short duration of the pre-treatment and to only the epidermis being affected by short term use of topical tretinoin.[12] Topical tretinoin impact on collagen synthesis requires a longer duration of treatment (10–12 months) as evidenced by histological specimens.[12-15] Of note, Kligman et al noted that use of 0.25% tretinoin cream every other night for 2 weeks produced similar clinical and histological improvement after 4–6 weeks to that obtained by nightly use of 0.05% tretinoin for 12 months.[16]

One reason for lack of statistical significance in our study may be the lack of statistical power. Another consideration is that a longer treatment period with tretinoin 0.05% lotion may be needed to see a significant difference between vehicle and the active ingredient. Future studies should involve a longer treatment period with topical tretinoin or a higher concentration of the topical agent to assess for efficacy.

CONCLUSION

In our study, patients tolerated the combination of 1927 nm TFL and 0.05% tretinoin lotion well and had a significant improvement of photodamage and pigmentation. However, combining 0.05% tretinoin lotion with 1927 nm TFL didn't result in statistically significant increased efficacy when compared to the 1927 nm TFL. Future studies are warranted to determine if altering the concentration and/or duration of tretinoin treatment pre- and post- non-ablative laser treatment will change the outcome.

DISCLOSURES

The authors have no relevant disclosures.

Funding: This study was sponsored by Solta Medical, Inc.

REFERENCES

1. Farage M, Miller K, Elsner P, Maibach H. Intrinsic and extrinsic factors in skin ageing: a review. *Int J Cosmet Sci.* 2008;30(2):87-95.
2. Polder KD, Bruce S. Treatment of melasma using a novel 1,927-nm fractional thulium fiber laser: a pilot study. *Dermatol Surg.* 2012;38(2):199-206.
3. Brauer JA, McDaniel DH, Bloom BS, Reddy KK, Bernstein LJ, Geronemus RG. Nonablative 1927 nm fractional resurfacing for the treatment of facial photopigmentation. *J Drugs Dermatol.* 2014;13(11):1317-1322.
4. Darlenski R, Surber C, Fluhr J. Topical retinoids in the management of photodamaged skin: from theory to evidence-based practical approach. *Br J Dermatol.* 2010;163(6):1157-1165.
5. Tyring SK, Kircik L, Pariser DM, et al. The effects of once-daily tretinoin 0.05% lotion on quality of life in patients with moderate-to-severe acne vulgaris. *Am J Clin Dermatol.* 2020;21(6):891-899.
6. Kircik LH, Draelos ZD, Berson DS. Polymeric emulsion technology applied to tretinoin. *J Drugs Dermatol.* 2019;18(4):S148-S154.
7. Hevia O, Nemeth AJ, Taylor JR. Tretinoin accelerates healing after trichloroacetic acid chemical peel. *Arch Dermatol.* 1991;127(5):678-682.
8. Mandy SH. Tretinoin in the preoperative and postoperative management of dermabrasion. *J Am Acad Dermatol.* 1986;15(4):878-879.
9. Woodhall KE, Goldman MP, Gold MH, Biron J. Benefits of using a hydroquinone/tretinoin skin care system in patients undergoing intense pulsed light therapy for photorejuvenation: a placebo-controlled study. *J Drugs Dermatol.* 2009;8(9):862-867.
10. Orringer JS, Kang S, Johnson TM, et al. Tretinoin treatment before carbon-dioxide laser resurfacing: a clinical and biochemical analysis. *J Am Acad Dermatol.* 2004;51(6):940-946.
11. West TB, Alster TS. Effect of pretreatment on the incidence of hyperpigmentation following cutaneous CO2 laser resurfacing. *Dermatol Surg.* 1999;25(1):15-17.
12. Bhawan MD J. Short-and long-term histologic effects of topical tretinoin on photodamaged skin. *Int J Dermatol.* 1998;37(4):286-292.
13. Griffiths C, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *New Engl J Med.* 1993;329(8):530-535.
14. Kligman AM, Grove GL, Hirose R, Leyden JJ. Topical tretinoin for photoaged skin. *J Am Acad Dermatol.* 1986;15(4):836-859.
15. Green LJ, McCormick A, Weinstein GD. Photoaging and the skin: the effects of tretinoin. *Dermatol Clin.* 1993;11(1):97-105.
16. Kligman DE, Sadiq I, Pagnoni A, Stoudemayer T, Kligman A. High-strength tretinoin: a method for rapid retinization of facial skin. *J Am Acad Dermatol.* 1998;39(2):S93-S97.

AUTHOR CORRESPONDENCE

Rawaa Almukhtar MD MPH

E-mail:..... ralmukhtar@clderm.com

ITCH-SCRATCH-
ITCH-SCRATCH-
ITCH-SCRATCH-

THE ONE-OF-A-KIND
TOPICAL JAK INHIBITOR

NEW for uncontrolled, mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥12 years[1]

- **Clear or almost clear skin** (IGA 0/1)* in >50% of patients at week 8 (53.8% vs 15.1% and 51.3% vs 7.6% vehicle†; *P*<0.0001)[1,2]
- **Meaningful itch relief** (Itch NRS4) in >50% of patients at week 8 (52.2% vs 15.4% and 50.7% vs 16.3% vehicle†; *P*<0.0001)[1,2‡]
  - **Itch NRS4 response seen as early as day 3** (18.4% OPZELURA vs 4.2% vehicle and 13.2% OPZELURA vs 0% vehicle†)[3]

OPZELURA was studied in 1249 adult and adolescent patients ≥12 years of age in 2 identically designed double-blind, randomized, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2). In both studies, patients had an affected BSA of 3%-20% and an IGA score of 2 or 3 on a severity scale of 0-4. Patients were randomized to monotherapy with OPZELURA or vehicle BID for 8 weeks.[1,2]

*With a ≥2-grade improvement from baseline.[1]

†In TRuE-AD1 and TRuE-AD2, respectively.[1,2]

‡≥4-point improvement in NRS among patients with a score of ≥4 at baseline.[1]

BID=twice daily; BSA=body surface area; IGA=Investigator's Global Assessment; JAK=Janus kinase; NRS=numeric rating scale.

Discover the difference at OpzeluraHCP.com

Incyte Dermatology

INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections.

If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information on following pages.

Opzelura™
(ruxolitinib) cream 1.5%

IMPORTANT SAFETY INFORMATION for OPZELURA™ (ruxolitinib) cream 1.5% (continued)

SERIOUS INFECTIONS (continued)

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

Please see Brief Summary of Full Prescribing Information on following pages.

References: 1. Opzelura. Prescribing Information. Incyte Corporation; 2021. **2.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* Published online May 3, 2021. doi:10.1016/j.jaad.2021.04.085. **3.** Data on file. Incyte Corporation. 2021.

Incyte Dermatology

OPZELURA is a trademark of Incyte.
Incyte and the Incyte logo are registered trademarks of Incyte.
© 2021, Incyte Corporation. MAT-ONA-00101 09/21

Opzelura™ (ruxolitinib) cream 1.5%

Opzelura™ (ruxolitinib) cream 1.5%

OPZELURA™ (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD); the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Thrombocytopenia, Anemia and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to 60 grams per week.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose *[see Use in Specific Populations]*.

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

OPZELURA is a trademark of Incyte. All rights reserved.
U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 9079912; 9974790; 10639310; 10610530; 10758543; 10869870
© 2021 Incyte Corporation. All rights reserved
Issued: September 2021 PLR-ONA-00004

doi:10.36849/JDD6383

November 2021 1185 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Therapeutic Approaches and Special Considerations for Treating Molluscum Contagiosum

Lawrence F. Eichenfield MD,[a] Adelaide A. Hebert MD,[b] Anthony J. Mancini MD,[c] Theodore Rosen MD,[d] Jonathan Weiss MD[e]

[a]Rady Children's Hospital-San Diego and Departments of Dermatology and Pediatrics, University of California San Diego School of Medicine, San Diego, CA
[b]University of Texas Health Science Center Houston, Houston, TX
[c]Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago, IL
[d]Department of Dermatology, Baylor College of Medicine, Houston, TX
[e]Gwinnett Clinical Research Center, Inc., Snellville, GA

ABSTRACT

Molluscum contagiosum (molluscum) is a common skin condition, especially in children, yet treatment approaches by US health care practitioners vary widely. A dearth of clinical data from large, well-controlled studies has resulted in significant gaps in knowledge, including treatment guidelines and algorithms. As of this writing, there are no FDA-approved treatments for molluscum.

The objective of this review is to provide practitioners with expert, evidence-based information and guidance about treatment approaches for, and the special circumstances faced by, patients with molluscum. To this end, a group of five pediatric and adult dermatologists collectively identified treatments and special considerations they felt were most commonly used to treat molluscum. Hence, in the first part of the review, seven treatment approaches identified as the most important to review (e.g., curettage, cantharidin) are discussed in terms of their mechanisms of action, supporting clinical data, and rationale for use. Each treatment approach concludes with a "clinical pearls" section, which summarizes the group's experiences with the treatment. In the second part, five special considerations (e.g., atopic dermatitis, skin of color) are discussed with supporting clinical data and are also followed by a "clinical pearls" summary.

J Drugs Dermatol. 2021;20(11):1185-1190. doi:10.36849/JDD.6383

INTRODUCTION

Molluscum contagiosum (molluscum) is the third most common viral skin infection in children and one of the five most prevalent skin diseases worldwide.[1,2] Molluscum primarily affects children, the immunocompromised, and sexually active adults,[3] with the greatest incidence in children between the ages of 1 and 14.[4] While prevalence rates vary widely in the literature, best estimates range between 5.1% and 11.5%.[5]

Frequently described as "benign" and "self-limiting," molluscum is often perceived as a mild, short-lived illness that can be waited out. This perception is being challenged as new data about prognosis and impact on quality of life become available. The largest cohort study to date found that, not only was the average duration of illness more than a year, but, for a subpopulation of molluscum patients, especially those with larger numbers of lesions and those with higher CDLQI scores, the impact on quality of life was significant.[4]

Despite identification of molluscum nearly two centuries ago,[3] as of this writing, there are no treatments approved by the U.S. Food and Drug Administration (FDA),[1] nor is there consensus on the optimal treatment paradigm. While several excellent reviews of treatment options for molluscum have been published recently,[6-9] clinical guidance remains limited in the United States. The goal of this review was to collect and summarize both evidence- and experience-based information about treatments and considerations for special clinical presentations.

To this end, a group of pediatric and adult dermatologists widely recognized for their expertise in treating molluscum contagiosum convened to collectively discuss their treatment approaches. In Part I, the group identified seven therapies used frequently today and provided insights gained from their decades of experiences. In Part II, the group identified and discussed the key considerations for five clinical presentations frequently encountered when treating patients with molluscum.

PART I: THERAPEUTIC APPROACHES

Overview

Perhaps due to the lack of an FDA-approved treatment, many interventions have been reported for patients with molluscum; nearly 40 were included in the most recent Cochrane Review.[6] In Part I, the authors selected seven treatment approaches and discussed the merits and risks of each. Treatments are presented in alphabetical order.

Active Non-Intervention

Active non-intervention is an approach during which the physician, patient, and caregivers proactively decide to wait for spontaneous resolution of the infection.[6] Some practitioners (especially primary care providers) believe this to be the safest and most practical strategy, especially for immunocompetent patients without other comorbidities. The merit of this approach is being challenged as more is learned about disease course and impact.[3,4,6,10-12] The largest cohort study to date found that the average duration of infection was 13.3 months and that 30% and 13% of cases remained unresolved at 18 and 24 months, respectively.[4] Approximately 28% of patients experienced a moderate impact on their quality of life (CDLQI >7) while 10% experienced a large impact (CDLQI >13). The study's authors recommended that "active treatment should be considered for some children, especially those with larger numbers of lesions and those with higher CDLQI scores."[4]

Active Non-Intervention Clinical Pearls

The group felt that discussing the option of active non-intervention with caregivers and patients is important, in part to support their pediatric colleagues who often recommend this approach. However, explaining the data on persistence at one year and beyond, as well as co-infection rates, is equally important. In the group's experience, this option is one that many caregivers and adult patients will not accept because they are frustrated by the protracted duration of infection or because transmission or autoinoculation has occurred.

In the experience of the group's adult dermatologists, many patients with molluscum have lesions on or near the genitalia and should be informed that the lesions are contagious and therefore, the patient caught them from and could transmit them to another person. These patients typically reject non-intervention as a viable strategy.

Some experts will not advocate for active treatment if a patient is exhibiting the BOTE ("beginning of the end"; characterized by edema and erythema of the lesions) sign, as this is a sign of imminent resolution. In this instance, non-intervention may be the correct strategy. One dermatologist in the group provides the patient with sample tubes of a retinoid and requests a return visit in six weeks (as opposed to watchful waiting). The explanation provided to parents/patients is that the molluscum may be getting ready to resolve and can be "helped along" (by the retinoid treatment).

Cantharidin

Compounded cantharidin has been used to treat molluscum contagiosum and warts for more than 60 years.[13] Topical application of a liquid formulation in collodion via cotton swabs or toothpick produces intraepidermal blisters that destroy the lesions. Treatment regimens vary widely in the literature.

As cantharidin currently must be compounded, there is a lack of standardized and optimized manufacturing processes and formulations.[14,15] The first clinical development program of a cantharidin-based therapeutic was completed in 2020 with the positive outcomes of two large-scale, randomized, placebo-controlled Phase 3 clinical trials of VP-102 (cantharidin) topical solution, 0.7% (w/v) in children and adults with molluscum.[16] The company is currently pursuing approval by FDA.

Cantharidin Clinical Pearls

As children are the major constituent of the patient population, each expert has developed stress reduction techniques for administration. Stating that the treatment is painless is critical and can be reinforced by starting with a lesion that is visible to the patient and by applying a plain wooden applicator stick or water-moistened swab first to physician's skin and then to the parent/guardian's skin, before moving on to the child. One method to involve (and thus distract) a pediatric patient is to ask that they help by holding the clean applicators during administration. One pediatric dermatologist refers to the solution as "magic stinky water."

When setting expectations, the physician should explain that blisters are expected and will be similar in level of discomfort to blisters that develop when wearing new shoes. Caregivers/patients should be advised that several treatment sessions will likely be necessary. This is an important consideration for patients attending college or working, for whom "one-trip" treatments like curettage may be preferable.

Cryotherapy/Liquid Nitrogen

Cryotherapy is inexpensive and efficient because it can be easily and rapidly applied during an office visit.[10,13,14] Applying liquid nitrogen to a molluscum lesion via a cotton-tipped swab or portable sprayer induces formation of intracellular and extracellular ice crystals that destroy the tissue, including the lesion, and disrupt cell membranes and circulation in the skin.[14] Common side effects include pain, bleeding, and blistering at the freeze site. As this modality is painful, it is poorly tolerated by younger children.[7,13,14,17]

Cryotherapy/Liquid Nitrogen Clinical Pearls

The group considers cryotherapy to be effective and efficient

because a solid, short freeze of the molluscum body is enough to eradicate most lesions. However, it should only be used in selective populations (i.e., mid-teens and older). The types of lesions this modality works well for include facial lesions (if the number of lesions is low), periocular lesions, and giant mollusca.

When cryotherapy is used in younger children (or even older children), a variety of techniques can be employed to distract from the pain and make the child less resistant to future treatments, such as applying an ice cube to the skin just prior to application, rapidly pouring the remaining liquid nitrogen onto the floor (for the "poof") and creating a "hand" by pouring the remaining nitrogen into a rubber glove.

Curettage

Curettage is the physical removal of a molluscum lesion by opening the epithelial surface of the papule with an instrument (e.g., curette, punch biopsy) to scrape out the viral core.[7,13] This simple and relatively inexpensive procedure produces instantaneous clearance of visible lesions,[14,17] however, even with anesthesia, the scraping and pressure against the skin are still detectable and may be poorly received by a child. While clinical data are limited, studies have found that the treatment's efficacy depends on the number and distribution of lesions, the skill of the operator, and the history of atopy or presence of active atopic dermatitis.[7,13,14,17,18]

Curettage Clinical Pearls

The group was unanimous regarding their infrequent use of curettage and several stated that, in their practice, curettage has been almost entirely supplanted by treatments like compounded cantharidin. This is due to the pain that occurs despite anesthesia, the bleeding, and the need to bandage every treated lesion.

A topical anesthetic can improve tolerability, although it can be impractical if there is a high surface area to treat. Following guidelines regarding the volume of topical anesthetic to use is important, especially in younger children, as there have been reports of toxicities including seizures and methemoglobinemia.[19] Strategies used to mitigate a child's anxiety and pain include the use of a topical anesthetic cream under a bandage(s) for up to 30 minutes before curettage or ice to the area just prior.

Homeopathic Therapies

Homeopathic therapies appeal to patients and caregivers because they are available without a prescription, can be applied at home, and are typically affordable. There is also the false perception among the lay public that "natural" products are potentially safer than "manufactured" products. A small number of uncontrolled studies have reported the use of homeopathic products such as lemon myrtle oil (*Backhousia citriodora*)[13,20] and tea tree oil (*Melaleuca alternifolia*) for molluscum.[21] Two homeopathic products marketed specifically for molluscum are ZymaDerm® and MolluscumRX™, although, like all products currently in use for molluscum, they are not FDA-approved and have limited clinical data to support efficacy and safety claims.

Homeopathic Therapy Clinical Pearls

In the authors' collective experience, many patients will already have tried homeopathic therapies before seeing a dermatologist and are thus ready to talk about in-office treatments. Education is important; explain that these "natural" products have not been studied in clinical trials and that they may be no better than letting the infection run its "natural" course. One author, in making the point that the safety data for these unstudied products is limited, informs families that tea tree products can lead to allergic contact dermatitis.

Imiquimod

Imiquimod is applied as a topical cream (5%) that must be washed off. Imiquimod is the only therapy for which guidance was offered by the 2017 Cochrane Review, which was that imiquimod is not more effective than vehicle and is probably more harmful than vehicle in terms of adverse events and thus is not recommended for molluscum.[6]

Imiquimod Clinical Pearls

The group was unanimous in their opinion that imiquimod is not appropriate as a first-line therapy. Two authors have contributed to studies used in the meta-analysis discussed above, and report that they no longer use imiquimod for molluscum. Another consideration is that imiquimod requires months of self-administration and patients, especially pediatric, will find adherence challenging.

For adult patients, one exception in favor of imiquimod's use may be concomitant genital warts. Treatment may achieve clearance of both sexually transmitted diseases. The authors have found this "two diseases/one product" strategy to be unreliable, however; despite significant imiquimod-induced inflammation, the warts have cleared while the molluscum lesions did not. If used, caution is advised due to the risk of deep ulcers, erosive cheilitis, pemphigus-like blistering, and oral ulcers. If imiquimod has caused or worsened irritation or molluscum dermatitis, a low potency hydrocortisone can be prescribed.

Topical Retinoids

Retinoids such as tretinoin, adapalene, and tazarotene have been used in dermatology for indications including acne, psoriasis, and chemoprophylaxis against skin cancer.[13] One hypothesized mechanism of action is via skin irritation (rather than peeling of the skin).[10] Alternatively, the mechanism may relate to a retinoid's ability to control abnormal growth and differentiation of keratinocytes.[13]

Topical Retinoids Clinical Pearls

The authors' use of retinoids is infrequent and their clinical experience variable when treating molluscum. Some state that, in their experience in treating molluscum, formulations of tazarotene may be useful, with the caveat that the degree of therapy-related inflammation and irritation was often untenable. For the authors who do use retinoids, they consider them to be add-on therapy for refractory cases.

PART II: SPECIAL CONSIDERATIONS

Atopic Dermatitis and Molluscum Dermatitis

Atopic dermatitis (AD) is an inflammatory skin disorder that usually occurs in childhood.[22] Approximately 10-12% of children and 7% of adults have atopic dermatitis.[10] AD causes skin barrier dysfunction, resulting in epidermal damage and increased susceptibility to pathogens. This susceptibility underlies the higher prevalence of molluscum in patients with AD.[22]

In patients with molluscum and AD, complications range from mild (e.g., hyperkeratosis, erythema) to intense (e.g., superinfection, severe pruritus, pain).[10] These patients typically have larger lesion burdens and are at greater risk for scar formation, so curettage is not recommended.[18] Immunomodulatory agents may be effective long-term treatments for AD, but may worsen the molluscum infection.[18]

When eczema develops around molluscum lesions, the condition is referred to as molluscum dermatitis or eczema molluscorum.[7] Estimates suggest that 9%–47% of patients with molluscum develop this condition, typically a month or more after the lesions appear.[6,7] This increases the risk of autoinoculation and transmission because these patches of eczematous lesions are particularly itchy.[6]

Atopic Dermatitis and Molluscum Dermatitis Clinical Pearls

Treatment of molluscum dermatitis is critical because it often exacerbates pruritus, which leads to autoinoculation and transmission. Eczematous reactions to molluscum can also trigger eczema flares. Some of the authors wait to treat molluscum lesions with a topical therapy (e.g., cantharidin) until the dermatitis has cleared, while others concurrently treat the dermatitis while proceeding with molluscum treatment. Some treat the dermatitis first to "clear up the background noise," followed by an evaluation for treatment of the molluscum infection. Others treat the molluscum at the initial visit and prescribe topical corticosteroids for the eczematous areas other than the molluscum lesions.

HIV

The incidence of molluscum in patients with human immunodeficiency virus (HIV) is higher than in the general population, ranging from 5% to 18%.[6,23] Molluscum lesions have been used as a biomarker for progression of HIV infection because lesion incidence increases when a patient's CD4 counts drop below 200/mm^3.[24] Clinical presentation and prognosis of molluscum are atypical in patients with HIV; lesions appear in uncommon locations such as the face and neck, are larger (>1 cm), and more numerous. As the skin infection progresses, it becomes increasingly resistant to treatment.[6,7] Treatments that cause bleeding or leave open wounds (e.g. curettage), should be avoided due to the risk of additional infection.[18]

HIV Clinical Pearls

The current practice of starting antiretroviral therapy early, as soon as HIV positivity is discovered, has greatly decreased the incidence of molluscum associated with HIV infection. Also, the availability of increasingly simple antiretroviral therapeutic regimens, coupled with wider acceptability of pre-exposure prophylaxis (PrEP), has decreased the incidence of molluscum in patients with HIV. As a result, when molluscum infection does occur, it rarely assumes the profuse number or exaggerated size of lesions that it once did. For these patients, cryosurgery is an effective option, possibly augmented by topical retinoid application or combined with a session or two of cantharidin application.

Pediatric Considerations

A patient's age is a significant factor when considering treatment approaches. For example, the differences between a toddler's and a teenager's perception of their skin infection and its impact on their quality of life are significant, as are the differences between their ability to understand the risks and benefits of individual treatment options, to tolerate pain, and to suppress scratching to proactively reduce autoinoculation and transmission.

Pediatric Considerations Clinical Pearls

A major pediatric consideration is co-infection in the family. Shared baths and fomites are important, though probably less so than the skin-to-skin contact that occurs during normal play. While it is likely the household has already been exposed by the time of diagnosis, there is no need to isolate the patient. Families may appreciate hearing that once the lesions have resolved, the immunocompetent individual is presumed immune to the virus. The issue of sexually transmitted diseases is relevant for adolescents, but generally not young children. In the authors' experience, teenagers and adults are motivated to get treated. Citing family co-infection rates (41% in the 2015 Olsen et al. study)[4] often makes the case for active therapy in younger children.

Skin of Color

Many skin conditions are common to people of color (e.g., Black, Asian, Hispanic/Latino, and Native American) and some conditions are more common in skin of color (SOC) compared

to white skin. Despite this, there is a dearth of knowledge regarding dermatologic diseases in people of color. The data are mostly limited to surveys and case reports, and these are primarily in Black and Asian patients, without formal reporting in Hispanics/Latinos and Native Americans.[25]

There are multiple contributing factors to this critical gap: underrepresentation of ethnic minorities in clinical research and overrepresentation of Caucasian patients who seek treatment. For example, of the approximately 36 million visits to U.S. dermatologists in 2000, 92% of patients were Caucasian. To the authors' knowledge, there are no data for SOC patients with molluscum, but in a study of AD, Black and Asian children appeared to have an increased prevalence and severity of AD compared to Caucasian children.[26]

Skin of Color Clinical Pearls

Main considerations for treating molluscum in SOC patients revolve around the tendencies to develop post-inflammatory hyper- and hypopigmentation from therapies and conditions that cause inflammation. One author explains to the family that, should post-inflammatory hyper- or hypopigmentation develop after treatment, it is not a scar, but rather a temporary skin discoloration. An analogy is the skin's reaction to accidentally touching a hot oven rack; the burn is the initial skin trauma and the brown line that forms later is the post-inflammatory mark that will eventually fade.

In terms of therapeutic options, cryotherapy should be used extremely judiciously in SOC patients, especially in cosmetically sensitive areas. For cantharidin, it is important that the solution be applied only to involved skin to prevent post-inflammatory dyschromia. Curettage should be limited and avoided in patients who are known keloid formers.

Ophthalmic Lesions

Ophthalmic molluscum lesions are comparatively rare, and may be incorrectly diagnosed by ophthalmologists.[27-29] Two retrospective analyses showed that 40% to 60% of ocular lesions could not be diagnosed by clinical examination alone and required histopathology.[28,29] Epidemiologically, the proportions are roughly equal for the incidence of single vs. multiple lesions, unilateral vs. bilateral locations, and gender. For immunocompromised adults, it has been proposed that ocular molluscum lesions be considered an initial manifestation of acquired immunodeficiency syndrome (AIDS). This hypothesis is supported by the finding that CD4+ counts in patients with HIV are inversely correlated with incidence of ocular lesions.[27]

The eyelid is the most common location of ophthalmic lesions, although lesions in the conjunctiva or cornea have also been reported.[10,29-31] Ocular lesions are frequently complicated by conjunctivitis or eczema, both of which resolve upon removal of the molluscum lesions.[6] Surgical removal is the most common intervention although topical solutions (e.g. ganciclovir) and cryotherapy have also been reported.[30]

Ophthalmic Clinical Pearls

Watchful waiting is advisable unless one of two conditions is met: 1) the lesions are bothersome and/or the patient wants them to be treated, or 2) larger lesions develop on the lid margin, which may cause ocular irritation or even corneal abrasion. If the patient exhibits a multi-site infection that includes ocular lesions, the other parts of the body may be treated with cantharidin with the explanation that the immune response is systemic and will help eradicate the ocular lesions over time.

For children who need extensive treatment, collaboration with colleagues in ophthalmology is important. If the lesions are symptomatic, ophthalmologists typically assist with the interventions. Treatment options include surgical removal or cryotherapy, but for young children, these procedures in this location typically require general anesthesia.

DISCLOSURES

Editorial support was provided by Versant Learning Solutions and funded by Verrica Pharmaceuticals Inc. The authors have received the following from Verrica Pharmaceuticals: Lawrence F. Eichenfield MD (H,C,S), Adelaide A. Hebert MD (H), Anthony J. Mancini MD (H), Theodore Rosen MD (H), Jonathan Weiss MD (H), and (H=honoraria; C=clinical funds; S=stocks).

REFERENCES

1. Shisler JL. Immune evasion strategies of molluscum contagiosum virus. *Adv Virus Res.* 2015;92:201-252.
2. Sterling J. Treatment of warts and molluscum: what does the evidence show? *Curr Opin Pediatr.* 2016;28(4):490-499.
3. Chen X, Anstey AV, Bugert JJ. Molluscum contagiosum virus infection. *Lancet Infect Dis.* 2013;13(10):877-888.
4. Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Time to resolution and effect on quality of life of molluscum contagiosum in children in the UK: a prospective community cohort study. *Lancet Infect Dis.* 2015;15(2):190-195.
5. Basdag H, Rainer BM, Cohen BA. Molluscum contagiosum: to treat or not to treat? Experience with 170 children in an outpatient clinic setting in the northeastern United States. *Pediatr Dermatol.* 2015;32(3):353-357.
6. van der Wouden JC, van der Sande R, Kruithof EJ, Sollie A, van Suijlekom-Smit LW, Koning S. Interventions for cutaneous molluscum contagiosum. *Cochrane Database Syst Rev.* 2017;5:CD004767.
7. Meza-Romero R, Navarrete-Dechent C, Downey C. Molluscum contagiosum: an update and review of new perspectives in etiology, diagnosis, and treatment. *Clin Cosmet Investig Dermatol.* 2019;12:373-381.
8. Robinson G, Townsend S, Jahnke MN. Molluscum Contagiosum: Review and Update on Clinical Presentation, Diagnosis, Risk, Prevention, and Treatment. *Current Dermatology Reports.* 2020:1-10.
9. Silverberg NB. Pediatric Molluscum: An Update. *Cutis.* 2019;104(5):301.
10. Silverberg N. Pediatric molluscum contagiosum: optimal treatment strategies. *Paediatr Drugs.* 2003;5(8):505-512.
11. Hughes WT. The athlete: an immunocompromised host. *Adv Pediatr Infect Dis.* 1997;13:79-99.
12. Hanna D, Hatami A, Powell J, et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol.* 2006;23(6):574-579.
13. Forbat E, Al-Niaimi F, Ali FR. Molluscum contagiosum: review and update on management. Pediatr Dermatol. 2017;34(5):504-515.
14. Gerlero P, Hernandez-Martin A. Update on the treatment of molluscum contagiosum in children. *Actas Dermo-Sifiliográficas (English Edition).* 2018;109(5):408-415.

15. Del Rosso JQ, Kircik L. Topical cantharidin in the management of molluscum contagiosum: preliminary assessment of an ether-free, pharmaceutical-grade formulation. *J Clin Aesthet Dermatol.* 2019;12(2):27-30.
16. Eichenfield LF, McFalda W, Brabec B, et al. Safety and efficacy of VP-102, a proprietary, drug-device combination product containing cantharidin, 0.7%(w/v), in children and adults with molluscum contagiosum: two phase 3 randomized clinical trials. *JAMA Dermatology.* 2020;156(12):1315-1323.
17. Sterling J. Treatment of warts and molluscum: what does the evidence show? *Curr Opin Pediatr.* 2016;28(4):490-499.
18. Nguyen HP, Tyring SK. An update on the clinical management of cutaneous molluscum contagiosum. *Skin Therapy Lett.* 2014;19(2):5-8.
19. Cho YS, Chung BY, Park CW, Kim HO. Seizures and Methemoglobinemia After Topical Application of Eutectic Mixture of Lidocaine and Prilocaine on a 3.5-Year-Old Child with Molluscum Contagiosum and Atopic Dermatitis. *Pediatr Dermatol.* 2016;33(5):e284-e285.
20. Burke BE, Baillie J-E, Olsen RD. Essential oil of Australian lemon myrtle (Backhousia citriodora) in the treatment of molluscum contagiosum in children. *Biomed Pharmacother.* 2004;58:245-247.
21. Markum. Combination of essential oil melaleuca and iodine in the treatment of MC in children ZYMADERM. 2012.
22. Manti S, Amorini M, Cuppari C, et al. Filaggrin mutations and Molluscum contagiosum skin infection in patients with atopic dermatitis. *Ann Allergy Asthma Immunol.* 2017;119(5):446-451.
23. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol.* 2000;43(3):503-507.
24. Robinson G, Townsend S, Jahnke MN. Molluscum Contagiosum: Review and Update on Clinical Presentation, Diagnosis, Risk, Prevention, and Treatment. *Current Dermatology Reports.* 2020;9(1):83-92.
25. Taylor SC. Epidemiology of skin diseases in people of color. *Cutis.* 2003;71(4):271-275.
26. Buster KJ, Stevens EI, Elmets CA. Dermatologic health disparities. *Dermatol Clin.* 2012;30(1):53-59, viii.
27. Rosner M, Zloto O. Periocular molluscum contagiosum: six different clinical presentations. *Acta Ophthalmol.* 2018;96(5):e600-e605.
28. Charteris D, Bonshek R, Tullo A. Ophthalmic molluscum contagiosum: clinical and immunopathological features. *Br J Ophthalmol.* 1995;79(5):476-481.
29. Mukherjee B, Vaidya H, Alam M. Clinical profile and management outcomes of periocular molluscum contagiosum. T*NOA Journal of Ophthalmic Science and Research.* 2020;58(1).
30. Serin S, Bozkurt Oflaz A, Karabagli P, Gedik S, Bozkurt B. Eyelid molluscum contagiosum lesions in two patients with unilateral chronic conjunctivitis. *Turk J Ophthalmol.* 2017;47(4):226-230.
31. Schornack MM, Siemsen DW, Bradley EA, Salomao DR, Lee HB. Ocular manifestations of molluscum contagiosum. *Clin Exp Optom.* 2006;89(6):390-393.

AUTHOR CORRESPONDENCE

Lawrence F. Eichenfield MD

E-mail:.....leichenfield@rchsd.org

doi:10.36849/JDD.0102

November 2021 1191 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

An Open-Label Pilot Study to Investigate Safety and Efficacy of Fixed Combination Tazarotene 0.045% and Halobetasol Propionate 0.01% Lotion for the Treatment of Scalp Psoriasis

Elif Ozyurekoglu and Leon H. Kircik MD[a]

[a]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC; DermResearch, PLLC; Skin Sciences, PLLC, Louisville, KY

ABSTRACT

Up to 80% of individuals with plaque psoriasis have scalp involvement, which can have a significant impact on the quality of life of affected individuals. Despite advancements in psoriasis therapeutics, management of scalp involvement remains a challenge. This12-week, open-label pilot study assessed the safety and efficacy of fixed combination tazarotene 0.045% and halobetasol propionate 0.01% lotion for the treatment of patients with mild-to-moderate plaque psoriasis with scalp involvement. Among 20 patients who were followed through 12 weeks, there were significant improvements in the primary endpoint (Investigator's Global Assessment (IGA)) and most secondary endpoints (Psoriasis Scalp Severity Index (PSSI), body surface area (BSA), and scalp IGA (sIGA)). Treatment was well-tolerated. Further placebo-controlled double-blinded study for confirmation of our results is recommended.

J Drugs Dermatol. 2021;20(11):1191-1194. doi:10.36849/JDD.0102

INTRODUCTION

Psoriasis is a common, chronic, autoimmune skin disorder that, in its plaque form, is characterized by dry, red lesions with silvery scales that cause itching, dryness, and irritation.[1] About 80% of psoriasis patients have scalp involvement, which can be challenging to treat. Systemic therapies, including biologics, may improve scalp psoriasis, although there is limited head-to-head comparative data assessing the effectiveness of biologics for scalp disease.[2,3] Additionally, not all patients are candidates for systemic therapy, and dermatology providers may not consider systemic therapy for patients with psoriasis limited primarily or exclusively to the scalp. Other treatments shown effective in the management of scalp psoriasis include phototherapy, topical medications, and even complementary and alternative medical interventions used to clear psoriasis or reduce symptoms; combination approaches are frequently employed.[4-7] These psoriasis treatment methods have been used with limited to moderate results for scalp involvement due to challenges associated with application, potential adverse effects, and high costs.[8,9] Topical products are difficult to use consistently to treat scalp psoriasis, especially due to hair on the affected area; application of topical medications can be arduous, messy, and inconvenient and can leave residue on the scalp and hair.[5] Long-term adherence with inconvenient regimens may be limited, leading to poor response or frequent relapse.[9,10] Importantly, it is recognized that scalp psoriasis can have a detrimental psychological impact upon patients, with many experiencing interpersonal stress and anxiety over displaying their symptoms publicly.[11,12] Therefore, it is desirable to identify effective interventions for scalp psoriasis.

Fixed combination tazarotene 0.045% and halobetasol propionate 0.01% (Duobrii, Ortho Dermatologics) lotion has recently been approved for treatment of moderate-to-severe plaque type psoriasis. The lotion base is suggested to confer benefits for application to the hair-bearing scalp. A pilot study was completed to evaluate the efficacy and safety of fixed combination tazarotene 0.045% and halobetasol propionate 0.01% for the treatment of moderate to severe plaque psoriasis with scalp involvement. There was significant improvement in the primary and most secondary endpoints, indicating that further study is warranted.

STUDY DESIGN

A single-center, open-label pilot study was designed to assess treatment with fixed combination tazarotene 0.045% and halobetasol propionate 0.01% lotion in adult subjects (age 18 or older) with moderate-to-severe plaque type, as indicated by an Investigator's Global Assessment (IGA) scale value of 3 or 4, with scalp involvement.

Subjects were provided study medication and instructed to apply the supplied formulation to all affected areas once daily and rub in gently and completely. The study duration was 12 weeks, with scheduled visits for screening at baseline, at week 4, week 8, and week 12 (end of study (EOS]). The study protocol was Institutional Review Board (IRB)-approved. The site carried out the study in keeping with local legal and regulatory requirements, abided by principles defined in the recognized "Guideline for Good Clinical Practice," and strictly followed ethical principles described in the current version of the Declaration of Helsinki.

Inclusion/Exclusion Criteria

The study enrolled adult subjects (≥18 years of age) of either gender. Females of child-bearing potential were required to have a negative urine pregnancy test within 7 days of the first dose of study drug and had to agree to practice a reliable method of contraception throughout the study. Subjects had to have moderate to severe overall psoriasis as well as moderate to severe scalp psoriasis to be included.

Subjects with spontaneously improving or rapidly deteriorating plaque psoriasis, as determined by the investigator, and those with guttate, erythrodermic, or pustular psoriasis were ineligible for enrollment. Additionally, subjects were not eligible for enrollment if they had used topical steroids, topical immunomodulators, topical vitamin D derivatives, tar, salicylic acid, anthralin, or any other topical treatment for scalp psoriasis within 2 weeks of baseline, any biologics within 3 months of baseline, or other systemic psoriasis treatments (ie, oral retinoids, methotrexate, cyclosporine, or other immunomodulators) within 4 weeks of baseline. Subjects who had undergone treatment with UVB or PUVA within 2 weeks of baseline were also ineligible. Subjects with known hypersensitivity to study medication or any of its components were excluded.

Study Evaluations

At each visit, IGA, Investigator's Global Assessment (sIGA), body surface area (BSA), Psoriasis Scalp Severity Index (PSSI), and physical examination, vital signs, prior and concurrent medications, tolerability and safety assessments, and urine pregnancy testing (where applicable) were performed. At baseline and week 4, drug dispensation was conducted, and at week 8, drug collection was conducted. Week 8 was the end of treatment and week 12 was the final visit for safety and maintenance after stopping the treatment at week 8.

The area of the body affected by psoriasis was estimated as a percentage of the subject's total body surface area. As a means to standardize measurements, the area of the subject's palm was considered as 1% of total BSA.

Efficacy Assessments

The primary endpoint is the percent of patients who are clear or almost clear on the investigator global assessment scale (IGA) at week 8.

Secondary endpoints include the percent of patients who are clear or almost clear on IGA at weeks 4 and 12; the percent of patients who achieved psoriasis scalp severity index (PSSI) 75 at weeks 4, 8, and 12; the body surface area assessment (BSA) improvement at weeks 4, 8, and 12; the scalp IGA (sIGA) improvement at weeks 4, 8, and 12; the visual analog score of pruritus (VAS) improvement at weeks 4, 8, and 12; local tolerability (itching, dryness, burning/stringing) at weeks 4, 8, and 12; and dermatology life quality index (DLQI) improvement at weeks 4, 8, and 12 were the secondary endpoints.

Subject compliance with the study treatment regimen was also assessed at each visit. Subjects complied with the restrictions based on prohibited medications and treatments as detailed in the exclusion criteria. The use of any concurrent medication, prescription or over-the-counter drug, was recorded along with the reason the medication was taken.

All subjects were monitored for adverse events (AEs), irrespective of causality.

Statistical Analysis

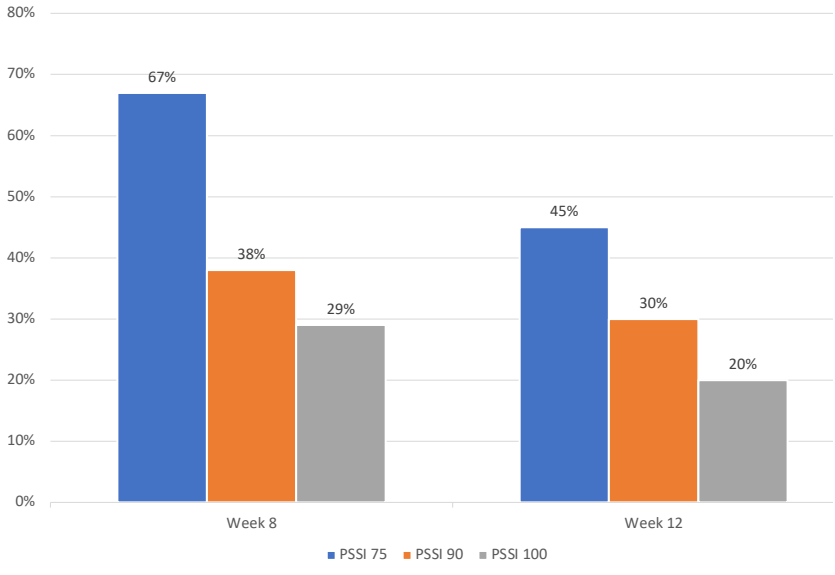
Statistical analyses were conducted on an intent-to-treat (ITT) population that included all subjects who were enrolled and received study medication. Due to the small sample size and exploratory nature of the study, descriptive statistics were performed using SAS. All statistical tests were two-sided and interpreted at a 5% significance level. Analyses of study treatment were performed using an ANCOVA technique with the baseline value as the covariate. Mean scores were also analyzed. Safety analyses were performed in terms of incidence and severity of local tolerance signs and symptoms and adverse and/or unexpected events.

RESULTS

A total of 21 subjects were included in the ITT data analysis. Of 21 patients enrolled in the study, 21 completed 8 weeks of therapy and 20 of 21 completed the 12-week follow-up visit. There were 12 males (57%) and 9 females (43%) enrolled, and 20 white (95%) and 1 African American (5%) subject. The average age at enrollment was 52 (SD = 17), with ages ranging from 24 to 86.

Treatment with fixed combination tazarotene 0.045% and halobetasol propionate 0.01% lotion resulted in significant reductions at each timepoint in the primary and most secondary outcome measures: the Investigator's Global Assessment (IGA), Psoriasis Scalp Severity Index (PSSI), body surface area (BSA), scalp IGA (sIGA). There were significant improvements in itching at weeks 4 and 8, burning at week 12, and the DLQI at week 8. There were 7 adverse events in 5 individuals, none of which was serious or of ongoing concern.

FIGURE 1. PSSI Scores



IGA Primary Endpoint

There were significant decreases in IGA from baseline at weeks 4, 8, and 12. At week 8, 10 of 21 (48%) patients were clear or almost clear (*P*=.0006; CI 95%). By week 12, after treatment discontinuation, 40% of subjects remained clear or almost clear (*P*=.004; CI 95%).

Secondary Endpoints

There were significant absolute and relative decreases in PSSI at weeks 4, 8, and 12. At week 4, 43% of subjects achieved PSSI 75, and 67% achieved PSSI 75 at week 8. At week 12, 45% of subjects maintained PSSI 75. PSSI 90 was achieved by 38% of respondents at week 8 and 30% maintained at week 12. PSSI 100 was achieved by 29% of respondents at week 8 and 20% maintained at week 12 after stopping the treatment at week 8.

Significant changes in BSA involvement were seen. Average BSA involvement decreased by 31% at week 4 (*P*=.0002), 47% at week 8 (*P*=.0003), and 34% at week 12 (*P*=.007; Figure 3).

At week 8 visit, 15 of 21 (72%) patients were clear or almost clear on the scalp IGA (CI 95%; SD 48%, 88%) and 50% maintained at week 12. More importantly, 29% of the subjects had all clear scalp at week 8 and 20% maintained all clear scalp at week 12.

There were significant absolute and relative improvements in DLQI measures at Week 8 and a significant absolute decrease at week 12.

Mean VAS for pruritus scores were decreased at weeks 4, 8, and 12, compared to baseline. However, neither absolute nor relative reductions in VAS achieved statistical significance at any timepoint. Tolerability assessments revealed significant decreases in itching at weeks 4 and 8 and in burning at week 12. Severe itch was reported by 7 patients at baseline and only 2 at week 12; 1 of 3 patients who reported severe burning at baseline continued to have severe burning at week 12. No patients reported severe of dryness. There were no reported instances of skin atrophy, striae, telangiectasia, or folliculitis.

FIGURE 2. % Change in BSA

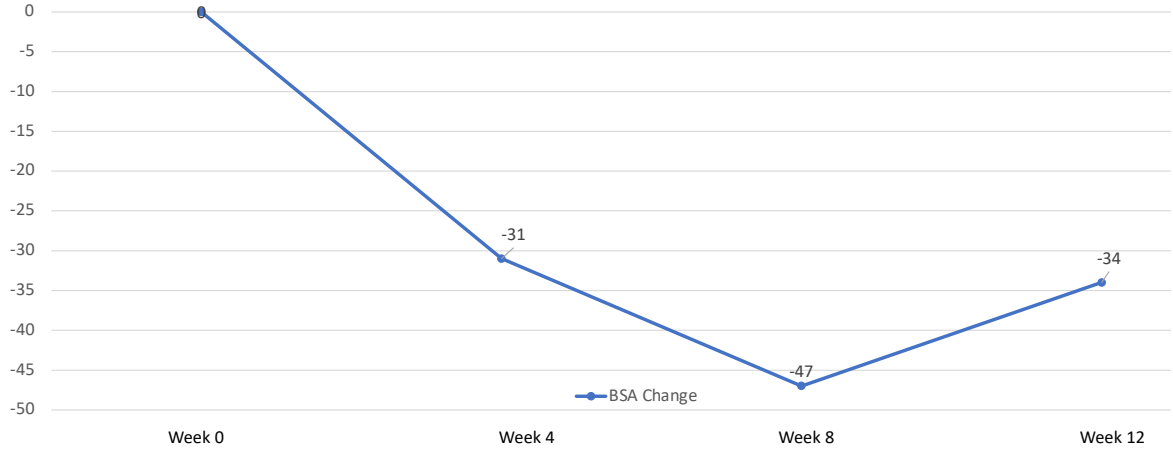
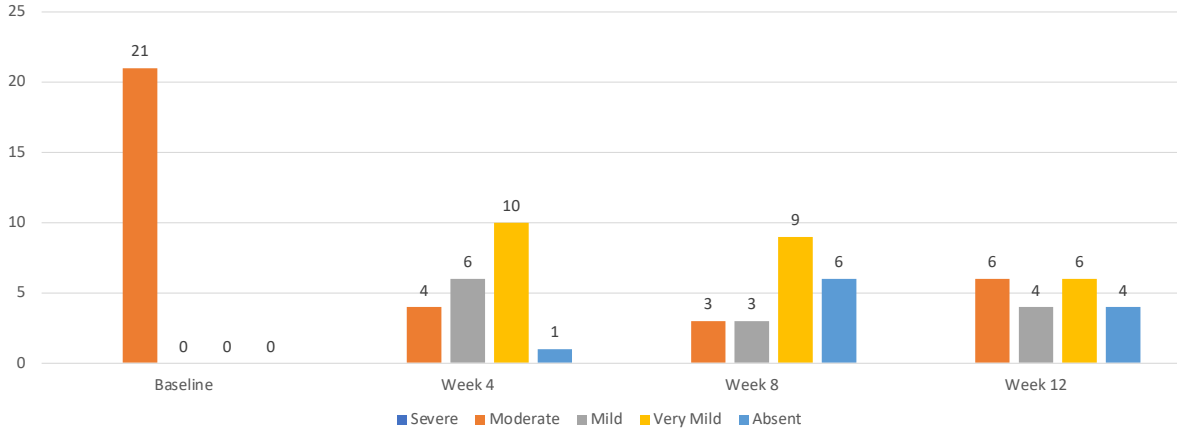


FIGURE 3. sIGA Ratings



Seven adverse events (AE) occurred in 5 subjects. None were serious and none appeared to be related to study medication. These included upper respiratory infection (resolved), type 2 diabetes, bilateral ear infection, generalized poison ivy (resolved), intermittent acute vertigo of peripheral origin, generalized muscle weakness, and worsening of acne.

CONCLUSION

Scalp psoriasis is a significant concern for affected patients, and treatment has remained challenging. Results of this pilot study demonstrate that fixed combination tazarotene 0.045% and halobetasol propionate 0.01% lotion is efficacious for the treatment of scalp psoriasis in adults, based on significant improvements in IGA, PSSI, BSA, sIGA, and DLQI. Treatment improved symptoms of itch and was well-tolerated. The type, frequency, and severity of AEs reported in this study suggest the safety of the medication for the treatment of scalp psoriasis. Additional studies are encouraged to further evaluate the use of fixed combination tazarotene 0.045% and halobetasol propionate 0.01% lotion to treat psoriasis with scalp involvement.

DISCLOSURES

Dr. Kircik has received either grant or honoraria compensation as either Speaker, Consultant, Investigator, or Advisory Board member for Abbott Laboratories, Abbvie, Allergan, Inc., Almirall, Amgen, Inc., Arcutis, Biogen-Idec, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Celgene, Centocor, Inc., Cellceutix, Cipher, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Eli Lilly, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Idera, Johnson & Johnson, Leo, Maruho, Merck, Medicis Pharmaceutical Corp., Novartis AG, Promius, PharmDerm, Pfizer, Serono (Merck Serono International SA), Stiefel Laboratories, Inc., Sun Pharma, Taro, UCB, Valeant Pharmaceuticals Intl, and XenoPort.

Funding: This study was funded by Ortho Dermatologics.

REFERENCES

1. Aldredge LM, Higham RC. (2018). Manifestations and management of Difficult-to-Treat Psoriasis. *J Dermatol Nurses Assoc,* 10(4), 189-197. https://doi.org/10.1097/JDN.0000000000000418
2. Camela E, Ocampo-Garza SS, Cinelli E, Villani A, Fabbrocini G, Megna M. Therapeutic update of biologics and small molecules for scalp psoriasis: a systematic review. *Dermatol Ther.* 2021 Mar;34(2):e14857. doi: 10.1111/dth.14857.
3. Alsenaid A, Ezmerli M, Srour J, Heppt M, Illigens BM, Prinz JC. Biologics and small molecules in patients with scalp psoriasis: a systematic review. *J Dermatolog Treat.* 2020 Jun 19:1-10. doi: 10.1080/09546634.2020.1770167
4. Bahraini P, Rajabi M, Mansouri P, Sarafian G, Chalangari R, Azizian Z. (2018). Turmeric tonic as a treatment in scalp psoriasis: A randomized placebo-control clinical trial. *J Cosmet Dermatol,* 17(3), 461–466. https://doi.org/10.1111/jocd.12513
5. Blakely K, Gooderham M. (2016). Management of scalp psoriasis: current perspectives. *Psoriasis (Auckland, N.Z.),* 6, 33–40. https://doi.org/10.2147/PTT.S85330
6. Wang TS, Tsai TF. (2017). managing scalp psoriasis: an evidence-based review. *Am J Clin Dermatol,* 18(1), 17–43. https://doi.org/10.1007/s40257-016-0222-4
7. Zhang P, Wu MX. (2018). A clinical review of phototherapy for psoriasis. *Lasers in Medical Science,* 33(1), 173–180. https://doi.org/10.1007/s10103-017-2360-1
8. Lebwohl M, Ali S. (2001). Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *J Am Acad Dermatol,* 45(4), 487-502. https://doi.org/10.1067/mjd.2001.117046
9. Murphy G, Reich K. (2011) In touch with psoriasis: topical treatments and current guidelines. *J Eur Acad of Dermatol Venereol,* 25(4), 3-8.
10. https://doi.org/10.1111/j.1468-3083.2011.04059.x
11. Sarma N. evidence and suggested therapeutic approach in psoriasis of difficult-to-treat areas: palmoplantar psoriasis, nail psoriasis, scalp psoriasis, and intertriginous psoriasis. *Indian J Dermatol,* 62,2 (2017): 113-122. doi:10.4103/ijd.IJD_539_16
12. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY, Gottlieb AB. (2016). Psoriasis. *Nat Rev Dis Primers,* 2. https://doi.org/10.1038/nrdp.2016.82
13. Leary MR, Rapp SR, Herbst KC, Exum ML, Feldman SR. (1998). Interpersonal concerns and psychological difficulties of psoriasis patients: Effects of disease severity and fear of negative evaluation. *Health Psychol,* 17(6), 530–536. https://doi.org/10.1037/0278-6133.17.6.530

AUTHOR CORRESPONDENCE

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

doi:10.36849/JDD.6219

November 2021 1195 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Importance of Skincare for Neonates and Infants: An Algorithm

Lawrence A. Schachner MD FAAD FAAP,[a] Anneke Andriessen PhD,[b] Latanya Benjamin MD FAAP FAAD,[c] Alanna F. Bree MD,[d] Peter A. Lechman MD MBA FAAP,[e] Ayleen A. Pinera-Llano MD,[f] Leon H. Kircik MD FAAD,[g] Adelaide Hebert MD FAAD[h]

[a]Pediatric Dermatology, University of Miami School of Medicine, Miami, FL
Department of Pediatrics, Leonard M. Miller School of Medicine, University of Miami, FL
[b]Radboud UMC, Nijmegen and Andriessen Consultants, Malden, The Netherlands
[c]Florida Atlantic University, Boca Raton, FL
[d]Baylor College of Medicine and Texas Children's Hospital, Houston, TX; A Children's House for Pediatric Dermatology, Houston, TX
[e]Northwestern Medical Group, Chicago, IL; Northwestern University Feinberg School of Medicine, Chicago, IL
[f]King Bay Pediatrics, Maimi, FL, General Pediatrics, Nicklaus Children's Hospital, Miami, FL
[g]Ichan School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC, Louisville, KY
[h]Departments of Dermatology and Pediatrics, UT Health McGovern Medical School, Houston, TX

ABSTRACT

Background: The skin of neonates and infants undergoes a maturation process from birth and is susceptible to barrier disruption. The current algorithm follows a US-based consensus paper on skincare approaches using gentle cleansers and moisturizers in neonatal and healthy infant skin. This summary provides clinical information for pediatric dermatologists, dermatologists, and pediatric healthcare providers treating neonates and infants.

Methods: The project used a modified Delphi process comprising virtual discussions followed by an online follow-up replacing the use of a questionnaire. During the virtual meeting, the systematic literature review results and a draft algorithm addressing over-the-counter skincare for neonates and infants with healthy skin were discussed and adopted using evidence coupled with the expert opinion and experience of the panel.

Results: The algorithm addresses three clinical signs: xerosis, erythema, and erosion/bulla. A growing body of evidence recognizes the benefits of ongoing daily use of non-alkaline cleansers and ceramides containing moisturizers to reduce inflammation and maintain a healthy skin barrier function. Diaper rash is common in infants presenting as erythema or, in more severe cases, skin erosion. Skin protection with a barrier cream and frequent diaper changes using disposable diapers resolves most cases; however, if the rash continuous despite appropriate care, rule out a *candida* infection.

Conclusion: The current algorithm focuses on neonatal and infant healthy skin that can benefit from skincare. When applied from birth onwards, gentle cleansers and moisturizers containing barrier lipids help maintain the protective skin barrier.

J Drugs Dermatol. 2021;20(11):1195-1205. doi:10.36849/JDD.6219

INTRODUCTION

At birth, human skin is structurally and functionally immature, with elevated skin surface pH, lower lipid content, and lower resistance to chemicals and pathogens.[1-5] From birth, the dynamic skin maturation process takes two years or longer, during which the neonate and infant skin is susceptible to barrier disruption.[1-3]

Compared to the adult stratum corneum (SC), the infant skin barrier is thinner and more subject to higher trans-epidermal water loss (TEWL) and skin conductance.[2-7]

The SC and supra-papillary epidermis structures were thinner in infants than adults in two systematic reviews, indicating a continuous structural maturation process of the infant skin.[6,7] These reviews further showed a functional maturation process of the infant skin expressed by a higher TEWL and elevated skin surface conductance values for infant skin than adults.[6,7]

Further studies comparing SC properties of infants and adults also showed higher TEWL and conductance rates and a significantly thinner supra-papillary epidermis for infants compared to adults at three months to twenty-four months.[2-4] These studies also showed that the proteolytic enzymatic activity was higher for infants than adult skin.[2-4]

In utero, the epidermis' final differentiation and the SC formation in the last trimester coincide with vernix caseosa covering the fetal skin surface.[8] The lipid content of vernix caseosa comprises cholesterol (52.8%), free fatty acids (27.7%), and ceramides (20.1%).[8] The vernix caseosa increases hydration, suppleness and decreases skin surface pH facilitating bacterial commensal development.[8-11]

Neonates and infants are particularly vulnerable to transcutaneous toxin exposure as they have a high surface-to-weight ratio, immature epidermis, and a compromised skin barrier.[12] Depending on systemic absorption, topical agents, which are harmless for adults, may cause respiratory distress, neurological toxicity, and even death in the neonatal and infants age groups.[13] Topical agents that may cause toxic reactions include isopropanol, benzocaine, pyrethrin, hexachlorophene, and salicylic acid, among others.[13]

During the skin's maturation process, the SC barrier of neonates and infants is especially vulnerable.[14] Exposure to common irritants, including saliva, nasal secretions, urine, feces, fecal enzymes, dirt, and microbial pathogens for long periods can lead to discomfort, irritation, infection, and skin barrier disruption.[14] Furthermore, the epidermal unsaturated fatty acids are easily extracted during cleansing, compromising SC barrier function.[15]

In neonatal and infant skin, the ratio of free fatty acids/cholesterol/ceramides (CERs) is not static.[14] Without the proper CERs ratio, the SC barrier function can become incompetent impairing barrier homeostasis, leading to dryness, irritation, erythema, and itching.[16]

There is a growing body of evidence supporting safe and effective skincare starting early in life. The evidence recognizes the benefits of ongoing daily use of non-alkaline cleansers and ceramides containing moisturizers to reduce inflammation and maintain skin barrier function.[14] When applied from birth onwards, gentle cleansers and moisturizers containing barrier lipids help maintain the protective skin barrier and soothe the skin with long-term moisturizing benefits.[14]

Scope

The current algorithm follows a US-based consensus paper on skincare approaches using gentle cleansers and moisturizers in neonatal and healthy infant skin.[14] The algorithm applies the recommendations discussed in the consensus paper to provide clinical information for pediatric dermatologists, dermatologists, and pediatric healthcare providers treating neonates and infants.[14] Other skin conditions that differ from neonatal and infant healthy skin are outside the scope of this publication.

MATERIALS AND METHODS

Literature Review

A systematic literature review explored present clinical guidelines and clinical research on skincare regimens for neonatal and infant healthy skin. Priority was given to studies addressing skin barrier function in newborns and infants and the clinical and quality of life (QoL) benefits of skincare in this population. Excluded were duplications, articles of insufficient quality [small sample size, poor methodology], and the latest version was used in the case of a review article. The results of the searches on 13–15 January 2020 for the consensus paper[14] were updated with searches on 01–02 October 2020. PubMed and on Google Scholar, as a secondary source, were searched for English-language literature (2010–2020) using the following terms:

Pediatric skin; maturation; skin physiology of neonates and Infants; vernix; infant skin barrier physiology; function; pathology; dysfunction; epidermal maturation's markers; erythema in neonates and infants; skin breakdown in neonates and infants; diaper care, umbilical cord care, protection infant skin barrier; fragility of epidermis in infants; depletion of stratum corneum lipids; cleansers; moisturizers; emollients; skincare in newborns and infants; ceramides; ceramide containing skincare; skin maturation and moisturization.

The selected publications were manually reviewed for additional sources by LS and AA and then graded using the American Academy of Dermatology evidence-based guideline development process.[17-19] For grading study type: A = clinical double-blind, randomized controlled trial [RCT] of high quality, B = RCT of lesser quality, and C = comparative trial with severe methodologic limitations.[19] For grading clinical evidence, four grades apply [1 = further research is unlikely to change confidence in the estimate of effect, to 4 = any estimate of effect is very uncertain].[19]

The searches yielded 106 papers deemed clinically relevant to healthy neonatal and infant skin, the use of over-the-counter (OTC) skincare, and ceramides containing skincare. After excluding duplicates and articles not related to neonatal and infant skin or OTC skincare, the summary included fifty-one publications. The selected articles comprised sixteen clinical studies (Table 1), fourteen systematic reviews, consensus papers or guidelines (Table 2), and twenty-one others.

Development of the Algorithm

The project used a modified Delphi process, a communication technique for interactive decision-making for medical projects.[17,18] The process entailed preparing the project, selecting the panel, and conducting systematic literature searches followed by two steps (Figure 1). Step 1 has been completed and yielded the consensus paper.[14]

TABLE 1.

Grading of Clinical Studies		
Reference	**Clinical Study Type**	**Grading**
Liu Q, et al, *Hindawi Biomed Research Int* 2018[1]	Cohort on infant barrier structure	B2
Nikolovski J et al, *J Invest Dermatol* 2008[2]	Clinical research study on barrier properties	C2
Fluhr JW et al, Br J Dermatol 2014[3]	Study on epidermal maturation markers in infancy	B2
Boiten WA et al, *J Lipid Research* 2018[8]	Study using tape-stripping and TEWL to assess lipid organization	C2
Dominguez-Bello MG et al, *Proc Natl Acad Sci USA* 2010[10]	Multiplexed 16S rRNA gene pyrosequencing to characterize bacterial communities from mothers and their newborn babies, four born vaginally and six born via Cesarean section	B2
Sahle FF et al, *Skin Pharmacol Physiol* 2015[16]	Research study on SC lipids and topical lipid substitution	B2
Younge NE et al, *Microbiome* 2018[24]	A cross-sectional study on preterm and term infants to characterize the skin microbiota	B2
Chittrock J et al, *Br J Dermatol* 2014[27]	Study on the development of SC protease activity and NMF from birth to 4 weeks of age compared to adults	A2
Kelleher M et al, *J Allergy Clin Immunol* 2015[32]	Skin barrier dysfunction in neonates predicts AD	B2
Lavender T et al, *J Obstet Gynecol Neonatal Nurs* 2013[33]	RCT including biophysical measurements on bathing with a cleanser and water versus water alone	A2
Garcia Bartels N et al, *Pediatr Dermatol* 2010[37]	RCT on neonatal skin barrier function	A2
Mack MC et al, *Pediatric Dermatol*[39]	Water-holding and transport properties of skin stratum corneum of infants and toddlers	A2
Yuan C et al, *BioMed Research Inter* 2017[40]	Developmental changes in ceramides and in protein secondary structure of the SC	A2
Kircik LH et al, *J Clin Aesthet Dermatol* 2011[42]	A sub-analysis of clinical efficacy and safety of a ceramide containing emulsion	B2
Lynde CW et al, *Cutis* 2014[43]	Cohort study using a ceramide containing cleanser and moisturizer in AD	B2
Gras-Le Guen C et al, *Pediatrics* 2017[49]	Dry care versus antiseptics for umbilical cord care	B2
	Total 16: A2:5, B2:9, C2:2	

A = Randomized, double-blind clinical trial of high quality
B = Randomized clinical trial of lesser quality
C = Comparative trial with severe methodologic limitations
1 = Further research is unlikely to change confidence in the estimate of effect
2 = Further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate
3 = Further research is very likely to have an important effect on confidence in the estimate of effect and is likely to change the estimate
4 = Any estimate of effect is very uncertain.

Step 2 comprised the development of the neonates and infants' skincare algorithm. To that end, the panel comprised of four pediatric dermatologists, one dermatologist, two pediatricians, and one basic scientist from the US convened a virtual meeting on February 5, 2021. The virtual discussion was followed by an online follow-up replacing the use of a questionnaire.[17] During this meeting, the systematic literature review results addressing OTC skincare for neonates and infants with healthy skin were discussed and adopted using evidence coupled with the expert opinion and experience of the panel. During the meeting in three small groups using virtual breakout rooms, the panel discussed and adapted the draft algorithm that was prepared by LS and AA based on the results of the literature searches. The breakout session was followed by presenting the three adapted versions of the algorithm to the group. An online process was then used to fine-tune the algorithm, reach consensus, and prepare and review a manuscript for publication.

The Algorithm

Figure 2A shows the algorithm which uses the Neonatal Skin Condition Score (NSCS), a validated scale to assess skin condition.[20] The NSCS includes three clinical signs: 1) Xerosis, 2) Erythema, and 3) Skin breakdown.[20] A 3-point scale is used to score the skin condition per sign [1 = normal, no signs, 2 = visible signs, 3 = extensive signs] (Table 3).[20] After scoring per sign, the total score for all three signs is calculated. A perfect score equals three, and the worst score equals nine. If a neonate or infant scores a single score of three of one sign area or a combined score of six and above, a physician must be notified. A dermatology referral may be appropriate in this case.[20-23]

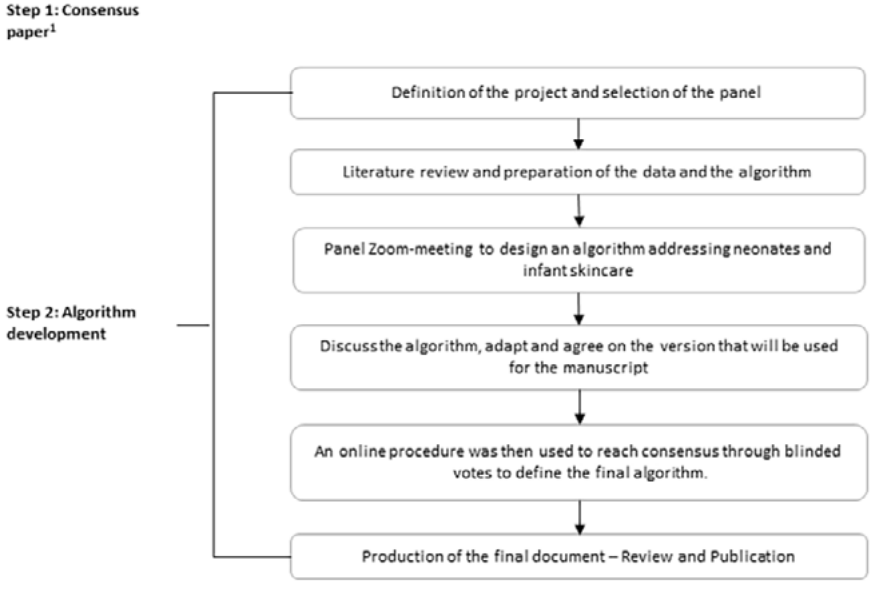
According to the panel, the NSCS scoring system initially developed to assess the skin condition of neonates is also applicable for infants. However, the cause of xerosis, erythema, and skin breakdown may be different.

TABLE 2.

Grading of Systematic Reviews, Guidelines, and Consensus Papers		
Reference	**Clinical Study Type**	**Grading**
Ludriksone et al, *Arch Dermatol Research* 2014[6]	Skin barrier function in infancy: A systematic review	A1
Kottner J et al, *Arch Dermatol Research* 2013[7]	Transepidermal water loss in young and aged healthy humans: a systematic review and meta-analysis	A1
Blume-Peytavi U et al, *Pediatr Dermatol* 2012[9]	Best practice review on skincare for neonates	B2
Cices A et al, *Am J Clin Dermatol* 2017[12]	Poisoning through pediatric skin	C2
Schachner et al, *J Drugs Dermatol* 2020[14]	Consensus on ceramide containing skincare for neonates and infants	C3
Alwood et al, *NPCHN* 2011[21]	Skincare guidelines for infant's 23–30 week 'gestation	C3
Cooke A et al, *British J Midwifery* 2018[34]	A systematic review and meta-analysis of skincare in newborns	B2
Blume-Peytavi U et al, *J Eur Acad Dermatol Venereol* 2009[35]	Consensus on bathing and cleansing in newborns	C2
Crozier K et al, *Evidence-Based Midwifery* 2010[36]	Structured literature review on skincare for neonates and infants	C3
Lynde CW et al, *J Drugs Dermatol* 2020[41]	A systematic review of SC pH in inflammatory conditions	C2
Clemison J et al, *Cochrane Database of Systematic Reviews* 2016[45]	A systematic review on cleansing products for neonatal skincare	B2
WHO 2014[47]	Postnatal Care of the Mother and Newborn	C3
Leante Castellanos JL et al, *An Ped* 2019[50]	Recommendations for umbilical cord care	C2
Schachner LA et al, *J Drugs Dermatol* 2021[51]	Consensus impetigo treatment and antimicrobial resistance	A2
	Total 14: A1:2, A2:1, B2:3, C2:4, C3:4	

Neonatal, Paediatric and Child Health Nursing (NPCHN)
A = Randomized, double-blind clinical trial of high quality
B = Randomized clinical trial of lesser quality
C = Comparative trial with severe methodologic limitations
1 = Further research is unlikely to change confidence in the estimate of effect
2 = Further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate
3 = Further research is very likely to have an important effect on confidence in the estimate of effect and is likely to change the estimate
4 = Any estimate of effect is very uncertain.

FIGURE 1. Steps in the process of algorithm development.



Step 1 of the process yielded publication of the consensus paper.[1]
The selected literature has to be clinically relevant to the algorithm.

FIGURE 2A. Algorithm for skincare in neonatal and infant skin.

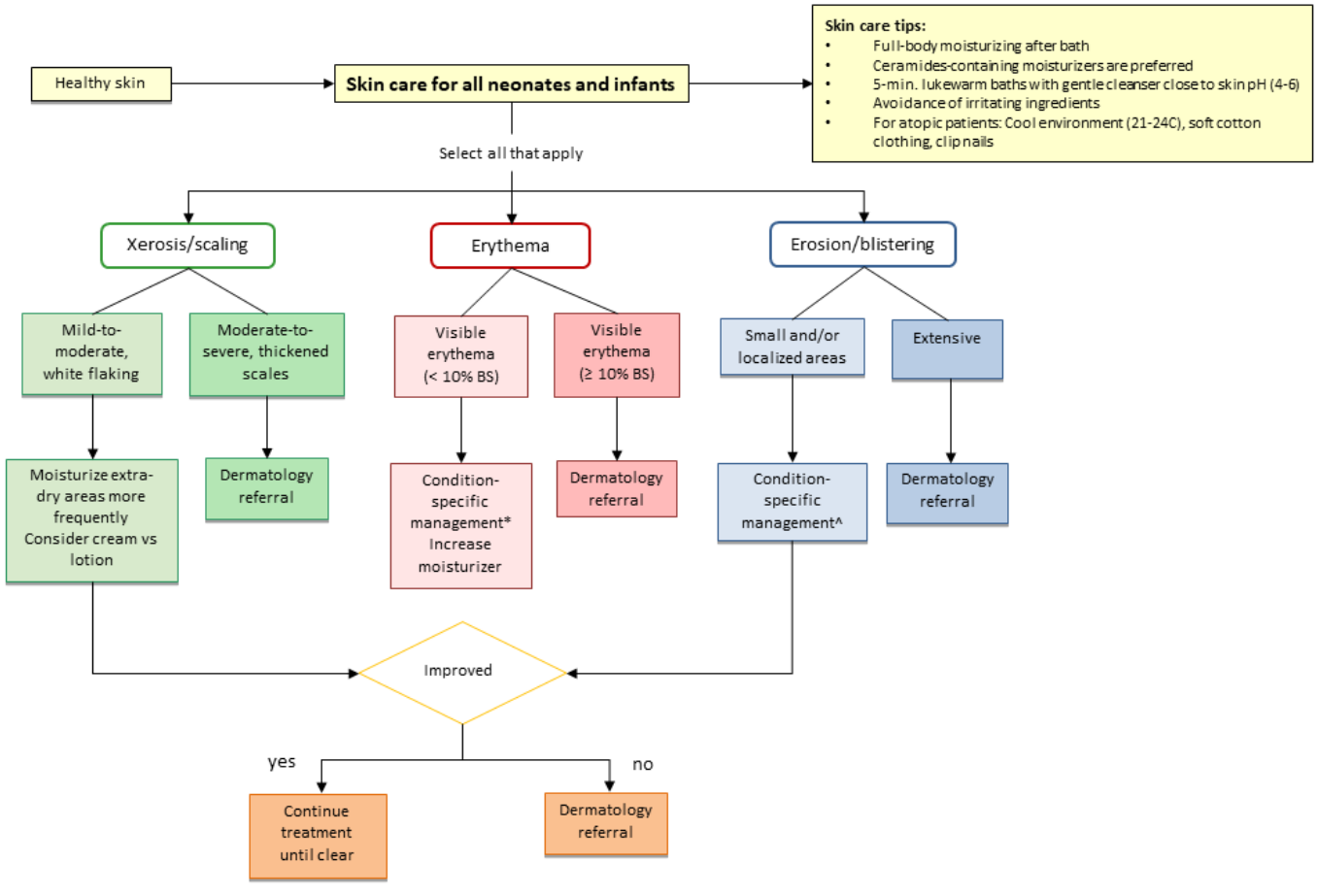


*Fig 2B, †Fig 2C
The scoring system of the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) and the National Association of Neonatal Nurses (NANN) (copyright 2018) was adapted from a visual scoring system (Lane & Drost, 1993).[20,21]

SC Differences Between Premature and Term Neonates

Term neonates have a well-developed SC containing 10–20 layers.[5,21] In premature neonates, depending on the neonate's gestation age, the SC may only have 2–3 layers.[5,21] The immaturity of the SC may result in increased moisture and heat loss leading to electrolyte imbalance, reduced thermoregulation, and increased infection risk.[3-6,21] Cohesiveness of the epidermis to the dermis differs in premature and term infants. Fibrils providing the cohesion between the epidermis and dermis are fewer and more widely spaced in preterm neonates.[3-6,21] This decreased cohesion increases the risk of skin injury, and thus the use of adhesives on the skin of neonates, especially premature babies, should be limited. If the adhesive used forms a stronger bond with the epidermis than the epidermis to the dermis, skin breakdown is likely.[21-23]

Differences in the skin surface pH also exist between premature and term newborns.[4-8,21] A slightly acidic skin surface plays an essential role in the maturation and maintenance of the SC, also inhibiting the growth of pathogenic microorganisms.[21] The vernix caseosa layer on the skin helps maintain skin hydration, thermoregulation, and skin acidification.[8] Premature infants of varying gestational ages and term infants are born with a more alkaline skin surface (pH >6.0).[21-23] For term infants, this usually falls to less than pH 5.0 within the first three days of life, providing a functional SC barrier.[21-23] Due to an immature skin structure and the reduced or negligible amount of vernix caseosa, the premature infant, has an alkaline skin surface for a more extended period.[5,8] The skin pH of a premature infant may take one week to decrease to pH 5.5 and up to a month to reach pH 5.1 and is therefore even more susceptible to xerosis, skin irritation, and infection at this time.[4,21-24]

An unbalanced skin microbiome may also play a role in the newborn period.[24]The skin microbiome in infants born vaginally has shown to be different from those delivered by Caesarean section. The clinical relevance of this finding needs further research regarding the potential of resultant dermatoses, which may benefit from skincare containing SC lipids such as ceramides.[14,16,24,25]

FIGURE 2B. Erythema specific management of neonates up to 11 months.

	Erythema	Clinical Features	Duration Treatment
	Erythema Toxicum Neonatorum	Various combinations of erythematous macules (flat red patches), papules (small bumps) and pustules.	Typically lasts for several days, requires no treatment.
	Miliaria	1–3 papules or vesicles. Location: typically, truncal and/or in areas of occlusion.	Remove from heated humid environment. Cool bathing or apply cool compresses. Topical steroids may be used to facilitate relief.
	Neonatal cephalic pustulosis Pityrosoprum Folliculitis	Erythematous dome shaped papules and superficial non-pruritic pustules arise in crops. Location: cheeks, nose and forehead, neck, upper chest.	Will resolve within weeks without treatment. If extensive, can treat with topical antifungals.
	Transient neonatal pustular melanosis	More common in infants with skin of color. Small pustules that resolve into hyperpigmented macules.	Gradually fade without treatment over several weeks to months.

The Neonatal Skin Condition Score[20,21] (NSCS) Erythema:
1 = no evidence erythema 2 = visible erythema 40% body surface 3 = visible erythema >SO% body surface

FIGURE 2C. Erosion and bullae specific management.

	Erythema	Clinical Features	Duration Treatment
	Mechanical trauma bullae (sucking, friction)	Bullae occur just below that stratum granulosum	Closed blisters cleanse the skin using a gentle cleanser and lukewarm water followed by the application of a moisturizer. For open blisters, a dressing may be needed. Select a dressing depending on the wound bed condition and exudate levels. Various dressings may be used, such as a foam dressing, a hydrofiber dressing or a non-adherent wound contact layer, including silicone-coated dressings.[48] The frequency of dressing change depends on exudate level.
	Burns and scalds	Painful erythema, bullae positiev capillary refill	On open burn, blisters cut the hydrofiber dressing to shape and leave in place until epithelialization is complete.
	Bullous scabies	Pruritic erythematous papules and burrows. Distinguish from diaper rash in ages 3–6 months.	Permethrin with two applications one week apart for infants older than 2 months of age. Lindane when there are concerns on neurotoxity.[46]

TABLE 3.

Neonatal Skin Condition Score		
Dryness	**Erythema**	**Breakdown**
1 = Normal, no signs of dry skin	1 = No evidence of erythema	1 = None evident
2 = Dry skin with visible scaling	2 = Visible erythema (<50% body surface)	2 = Small and/or localized areas
3 = Very dry skin with cracking and/or fissures present	3 = Visible erythema (>50% body surface)	3 = Extensive

Adapted from AWHONN guideline[20,21]
Interpretation of the results:
Perfect score = 3; Worst score = 9.
The relevant medical team must be notified if a neonate scores a single score of 3 in one area or a combined score of 6 and above. A dermatology referral may also be appropriate.

TABLE 4.

Types of Skin Cleansers		
Type of cleanser	**Description**	**pH**
Soap	Contains fat and alkali-treated salts of fatty acids	9.0–12.0
Syndet bar	Contains synthetic detergents	4.0–6.0
Combar	Contains equal parts of soap-based detergent mixed with a synthetic detergent	10.0–12.0
Liquid cleanser	Contains synthetic detergents, can be ionic or anionic in lotion, cream, oil, or gel form	6.0–7.0
Cleansers containing lipids that mimic physiological lipids	Non-soap-based cleaners containing synthetic detergents and lipids such as CERs	5.0–6.0

Adapted from Schachner et al[14]

Xerosis and Scaling in Neonates and Infants

The epidermal barrier is composed of corneocytes, held together with corneodesmosomes.[26,27] SC barrier function depends on the complex interplay among SC pH, desquamation rate, and the appropriate ratio of skin lipids.[16] The intercellular lamellar lipid membrane is primarily composed of CERs, cholesterol, and fatty acids, which play a vital role in SC hydration's physiological maintenance.[28,29] The SC lipids are composed of CERs (40–50%), cholesterols (20–33%), and free fatty acids (7–13%).[28,29] Other SC lipids include cholesterol-3-sulfate (0–7 %) and cholesteryl esters (0–20 %).[28,29] The SC contains numerous different CERs. The number of hydroxyl groups in the head group of the CERs appears to be playing a critical role in the SC barrier function.[28,29]

The importance of the individual structural features of CERs is not fully understood.[16,29,30] In neonatal and infant skin, the ratio of free fatty acids/cholesterol/CERs is not static.[14] Without the proper CERs ratio, the SC barrier function can become incompetent impairing barrier homeostasis, leading to dryness, irritation, erythema, and itching.[16]

Premature infants SC is deficient in essential fatty acids due to less fat-storing capacity.[21,31] SC lipid deficiency can present as superficial scaling of the skin and desquamation and irritation in the neck, groin, and perianal areas.[21,31]
Xerosis in infants may be indicative of a predisposition to AD. An impaired skin barrier function (measured as increased TEWL) assessed at birth and two months of age may precede clinical AD.[25,32]

The panel members agreed that prevention of AD is a broad topic that requires discussion of key studies and evidence beyond this algorithm's scope, which focuses on skin barrier function and the role of skincare in healthy neonates and infants.

Skincare

Skincare, including a gentle cleanser and moisturizer, is important in all neonates and infants and should begin immediately after birth, but must be safe and products must be appropriate for a newborn's skin based on its unique characteristics (Box 1).

Newborns and infants have a high surface-to-weight ratio, immature epidermis, and a compromised skin barrier, making them particularly vulnerable to transcutaneous toxin exposure.[12] Topical agents, which are harmless for adults, may cause respiratory distress, neurological toxicity, and even death in infants depending upon systemic absorption.[12] Topical agents that may cause toxic reactions include isopropanol, benzocaine, pyrethrin, hexachlorophene, and salicylic acid, among others.[12]

Skincare for neonates and infants should be safe, effective, fragrance and sensitizing agent-free. Skincare with CERs may benefit the stratum corneum's lipid and water content.[14]

Skin Hygiene and Cleansers

Bathing details are provided in Box 2. The frequency of bathing and time of day should be based on individual preference.[14]

Soaps, surfactants, and detergents, especially those with an alkaline pH, may excessively remove skin lipids, which is explicitly damaging to neonatal and infant skin.[14] Skin cleansers with a near physiologic skin surface pH (4.0–6.0) containing CERs and no soap are less irritating than alkaline soaps and may reduce skin irritation (Table 4).[9,14,15,21-23] When the skin is dried, corneocytes' rapid dehydration can lead to their release from the lipid matrix, creating cracks and facilitating penetration of

the surfactant to deeper layers.[15]

Box 1: Skincare tips

- Bathing (QD or QOD)
- Gentle cleanser with physiological pH
- Apply head-to-toe moisturizer after bath once daily for all infants
- Apply moisturizer more frequently for dryness, fissures, or flaking
- Maintain good hygiene by using one baby-specific container and a single-use applicator
- Provide a cool environment
- Use soft cotton clothing
- Clip nails regularly to avoid injury

A synthetic cleanser of non-ionic and amphoteric surfactants (pH around 5.5) was compared to water for skin cleansing of infants.[33] Biophysical and clinical measurements (TEWL, pH, SC hydration, dryness, erythema) revealed that both did not compromise SC integrity.[33] Various papers recommend that a pH-neutral, mild liquid cleanser is the preferred infant cleansing choice.[9,14,15,21-23]

Synthetic cleansers that do not contain soap may avoid adverse effects; however, robust evidence and clinical consensus on their use in neonates and infants are lacking.[33-38]

The inconsistent outcome measures hamper the available evidence on bathing, cleanser use versus water alone, and diaper care.[34]

The choice of cleanser and moisturizer is dependent on individual preference as long as the products used are free of fragrance and common sensitizers.[14]

The panel agreed that the advice that may be given to parents includes synthetic cleansers or liquid cleansers containing a mixture of fatty acids, cholesterol, and CERs.[14]

Box 2: Bathing

- Frequency of bathing and time of day should be based on individual preference
- Appropriate safety measures should be implemented
- Cleanse the bath with water before and after each use
- Water should be deep enough to allow the neonates shoulders to be well covered
- Cleansers should be free of potential irritants such as fragrance, alcohol, essential oils, botanicals (eg, lavender), and harsh detergents (eg, sodium lauryl sulfate)
- A neutral or mildly acidic (pH 4–6.0) cleanser may be used
- Maintain an adequately heated external environment, with an ideal room temperature of 21 – 24°C (close the doors to the room to minimise convective heat loss)
- Neonates and infants should be immediately covered with a towel and patted almost dry
- Ensure all skin folds are dried thoroughly (armpits, groin, neck, and behind the ears)
- A moisturizer is to be applied head to toe for skin dryness prevention and management

humectants, or emollients.[14] Moisturizers with occlusives, such as petrolatum, mineral oil, lanolin, olive oil, jojoba oil, etc, coat the SC and decrease TEWL.[14] Moisturizers with humectants can improve hydration of the SC, but in dry weather conditions can dry the skin further.[14] For that reason, these agents should be used together with occlusives.[14] Examples include glycerin, urea, hyaluronic acid alpha, beta hydroxy acids, propylene glycol, etc.

Emollients may include SC type lipids, such as CER, fatty acids, cetyl stearate, cholesterol, etc., which soften and smooth the skin by filling spaces between skin cells and creating a smooth skin surface.[14]

A systematic review and meta-analysis of evidence suggest that daily use of full-body emollient therapy may reduce the risk of AD in infants with a genetic predisposition to AD; however, the use of olive oil or sunflower oil for infant xerosis may adversely affect skin barrier function.[34]

Formulations that contain ceramides mimic physiological lipids supporting homeostasis and improving skin condition.[14,39-46] Those with dry and sensitive skin and particularly neonates and infants at risk for AD or having AD, greatly benefit from frequent moisturizer use (Box 3).[14] Moisturizer use decreases pruritus, symptoms, and the severity of AD, while also improving quality of life.[14,42,43,46] Moreover, the number of AD flares and the time to flaring is reduced when ceramide-containing skincare is frequently applied.[14,42,43,46]

Box 3: Moisturizer Use

- Apply a moisturizer head to toe daily once daily, for all infants
- Apply moisturizer more frequently for dryness, fissures or flaking of the skin
- Maintain good hygiene by using one baby-specific container and a single-use applicator
- Products should contain well- tolerated preservatives and be free of common sensitizers
- Moisturizers containing skin lipids such as CER may offer additional benefits

Erythema

Neonatal skin differs in structure and function from adult skin, and hence the dermatoses seen during this period differ in their clinical presentation. Depending on the etiology, various groups of dermatoses may be distinguished. For example, inherited or congenital disorders [Netherton syndrome, congenital ichthyosis, etc.], infectious diseases (herpes simplex, bullous impetigo, etc), and other skin fragility conditions may present uniquely in newborns.[21]

Most hereditary disorders with increased skin fragility may occur first during the neonatal period before four months of age, at an average of 7–9 weeks of life.[46] Congenital erythroderma is less common but is strongly suggestive of ichthyosis, Netherton syndrome, or immunodeficiency syndromes.[46]

Infectious disorders in neonates are rare.[46] Congenital cutaneous candidiasis arises from intrauterine exposure and presents as a inflammatory eruption with scattered pustules and rarely vesicles.[21,46-48] Lesions develop within the first six days of life, spreading from the trunk to acral sites, and can include the palms and soles. The lesions may rarely lead to life-threatening systemic infection and exfoliative erythroderma.[21,46-48]

Common types of erythema include erythema toxic neonatorum [ETN], miliaria, neonatal cephalic pustulosis [NCP], and transient neonatal pustular melanosis [TNPM] (Figure 2B).[21,22]

ETN is uncommon in premature neonates but affects about 30–50% of full-term babies. This condition arises in the first few days after birth and presents with scattered transient pink or red papules and wheals scattered over the face and the rest of the body, sparing the palms and soles. ETN does not cause discomfort and resolves spontaneously over one to two days.[21,22]

Transient neonatal pustular melanosis is a disorder in which macules and papules are present at birth.[21,22] The pustules show a mixture of neutrophils and some eosinophils and resolve with hyperpigmented macules that fade with time.[21] As in ETN the babies are otherwise well.

Miliaria affects about 15% of newborn babies in warm climates due to occlusion of the sweat duct. If the occlusion is superficial, sweat collects just below the SC forming clear, thin-walled blisters (miliaria crystallina). Slightly deeper occlusion results in red papules and pustules (miliaria rubra or 'prickly heat').[21,22] Miliaria most often affects the forehead, neck, and upper trunk and occluded skin areas of neonates in the first few weeks of life. The skin changes resolve within a few days on cooling and removing occlusive clothing.[21,22]

Neonatal cephalic pustulosis or Pityrosoprum folliculitis are none pruritic, erythematous papules, and superficial pustules presenting in crops commonly on the cheeks, nose, and forehead.[21,22] The condition results from an inflammatory reaction to Malessezia species on the skin and within the hair follicles which can be seen after birth and may relate to increased activity of the sebaceous glands.[21,22] It affects newborn infants in the first weeks of life and will resolve within weeks without treatment, but may resolve more quickly with topical antifungal agents.[21,22]

Erosion and Bullae

Severe conditions such as staphylococcus scalded skin syndrome, epidermolysis bullosa, eczema herpeticum, herpes simplex, and erosions are outside the scope of this algorithm.[46-48]

Newborns are more likely to develop bullae and erosions in response to heat, chemical irritants, and mechanical trauma and are at an increased risk for cutaneous infections.[9,14,21-23,48] As the SC barrier is maturing, neonates and infants are especially vulnerable.[14] Exposure to common irritants, including saliva, nasal secretions, urine, feces, fecal enzymes, dirt, and microbial pathogens for long periods can lead to discomfort, irritation, infection, and skin barrier disruption.[14] Furthermore, the unsaturated fatty acids are easily extracted during cleansing, compromising SC barrier function.[14,15,29]

Diaper rash is the most common skin condition in infants presenting as erythema or, in more severe cases, skin erosion.[21] The most common type of diaper rash is irritant dermatitis due to stool, urine, or mechanical irritation.[21] The groin folds are usually protected from urine and stool and therefore not affected.[21] If the rash is continuous despite appropriate care, rule out a *candida* infection.[21,48] If a *candida* infection is present, also check for oral candidiasis.[21,48] Details on diaper care are given in Box 4.

Box 4: Diaper Care

- Evaluation of the perineal area is required at each diaper change to ensure early identification of perineal dermatitis and infections
- Disposable diapers are preferred[8,21]
- In case of diarrhea increased frequency of diaper changes are required depending on the condition to every 1–4 hours
- Cotton balls or soft disposable towels with warm water are the preferred cleansing method
- A physiological pH (4-7) cleanser may be used if stools are dry and difficult to remove[8,21]
- Wipes should be avoided (if required they should be free from alcohol and fragrance)
- Barrier creams should be used on all neonates at every diaper change at the first sign of erythema or skin breakdown[8,21]
- The removal of barrier creams between diaper changes is not necessary, rather apply another layer. Barrier creams containing plant extracts and/or fragrance should be avoided[8,21]
- Risk factors for perineal dermatitis include: Frequent stooling; antibiotic use; malabsorption; opiate withdrawal; abnormal rectal sphincter tone[8,21]
- Avoid use of powders in diaper area

Umbilical cord care until its detachment remains controversial.[47,49,50] The World Health Organization advocates for dry cord care; however, the use of chlorhexidine on the stump is recommended when hygienic conditions are poor, and the risk for omphalitis is higher (Box 5).[47,49,50]

Box 5: Umbilical Cord Care

- Keep the cord area clean with water[47,49,50]
- Use chloorhexidine on the cord to avoid infection when hygienic conditions are insufficient[47,49,50]
- Fold the diaper down below the umbilicus
- Cord clamp may remain in place until separation
- Where possible the umbilical stump should be kept exposed to air or loosely covered with clean clothing to avoid irritation and promote healing
- Avoid exposing the periumbilical skin to chemicals in order to prevent periumbilical burns[47,49,50]
- Regular assessment is necessary to ensure normal umbilical cord healing and to identify potential problems including infection

heat, chemical irritants, and mechanical trauma that are small and or localized.[9,14,21-23,44,48]

Due to mechanical trauma such as caused by repeated friction, bullae develop just below the stratum granulosum.[48] Burns and scalds can be accidental or intentional in the case of child abuse. A careful history and physical examination with attention to the child and caregiver interactions is needed.[48] In inflicted burns, there is often a delay in seeking care from healthcare professionals, therefore look for lesions in various stages of healing and also with unusual patterns or locations.[48]

Neonates and infants with skin erosions are particularly at risk for infection, especially as their skin is immature.[3-6,21] For closed bullae, cleanse the skin using a gentle cleanser and lukewarm water followed by the application of a moisturizer while leaving the bullae intact. A wound dressing may be required for open bullae. Select a dressing depending on the wound bed condition and exudate levels. Various dressings may be used, such as a foam dressing, a hydrofiber dressing, or a non-adherent wound contact layer, including silicone-coated dressings. The frequency of dressing changes depends on exudate level and are typically twice/week (Figure 2C). For infants at risk for infection, use an antiseptic cleanser, such as chlorhexidine aqueous solution. Avoid the use of prophylactic topical antibiotics to comply with antimicrobial stewardship preventing antibiotic resistance.[51]

LIMITATIONS

Although limited evidence was available to guide the development of the algorithm, the project will hopefully spur more skincare studies in neonates and infants. Until then, we kno wit is important to maintain a healthy skin barrier, which is accomplished by using skincare products that are sensitizer and fragrance free and also containing lipids, such as ceramides.

CONCLUSONS

The algorithm focuses on neonatal and infant healthy skin that can benefit from skincare. A growing body of evidence recognizes the benefits of ongoing daily use of non-alkaline cleansers and ceramides containing moisturizers. When applied from birth onwards, gentle cleansers and moisturizers containing barrier lipids help maintain the protective skin barrier.

DISCLOSURES

The authors disclosed receipt of an unrestricted educational grant from CeraVe USA for support with the research of this work.

REFERENCES

1. Liu Q, Zhang Y, Danby SG, Cork MJ, Stamatas GN. Infant skin barrier, structure, and enzymatic activity differ from those of adults in an East Asian cohort. *Hindawi Biomed Research Int* 2018;7:1-8. https://doi.org/10.1155/2018/1302465
2. Nikolovski J, Stamatas GN, Kollias N, Wiegand BC. Barrier function and water-holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol* 2008;128(7):1728–36.
3. Fluhr JW, Lachmann N, Baudouin C, et al. development and organisation of human stratum corneum after birth: Electron microscopy isotropy score and immunocytochemical corneocyte labeling as epidermal maturation's markers in infancy. *Br J Dermatol* 2014;171(5):978–86.
4. Fluhr JW, Darlenski R, Lachmann N, et al. Infant epidermal skin physiology: adaptation after birth. *Br J Dermatol* 2012;166:483–490.
5. Visscher MO, Narendran V. Neonatal infant skin: development, structure and function. *Newborn Infant Nursing Reviews* 2014;14(4):135-141.
6. Ludriksone L, Garcia Bartels N, Kanti V, Blume-Peytavi U, Kottner J. Skin barrier function in infancy: A systematic review. *Arch Dermatol Research* 2014;306(7):591–599.
7. Kottner J, Lichterfeld A, Blume-Peytavi U. Transepidermal water loss in young and aged healthy humans: a systematic review and meta-analysis, *Arch Dermatol Research* 2013;305(4):315–323.
8. Boiten WA, Berkers T, Absalah S, et al. Applying a vernix caseosa based formulation accelerates skin barrier repair by modulating lipid biosynthesis. *J Lipid Research* 2018;59(11):259-260. http://www.jlr.org
9. Blume-Peytavi U, Hauser M, Stamatas GN, et al. Skin care practices for newborns and infants: review of the clinical evidence for best practices. *Pediatr Dermatol* 2012;29:1– 14.
10. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* 2010;107:11971–11975.
11. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science* 2009;324:1190–1192.
12. Cices A, Bayers S, Verzi AE, Schachner LA, West DP, Micali G. Poisoning through pediatric skin. *Am J Clin Dermatol* 2017;18(3):391-403.
13. Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. *Ann Allergy Asthma Immunol* 2018;120(2):145-151.
14. Schachner LA, Andriessen A, Benjamin L, et al. A Consensus about the Importance of Ceramide containing Skincare for Normal and Sensitive Skin conditions in Neonates and Infants. *J Drugs Dermatol* 2020;19(8):769-776. DOI: 10.36849/jdd.2020.5252 PMID: 32845590
15. Ananthapadmanabhan KP, Mukherjee S, Chandar P. Stratum corneum fatty acids: their critical role in preserving barrier integrity during cleansing. *Int J Cosmetic Science* 2013;35(4):337-345.https://doi.org/10.1111/ics.12042)
16. Sahle FF, Gebre-Mariam T, Dobner B, Wohlrab J, Neubert RH. Skin diseases associated with the depletion of stratum corneum lipids and stratum corneum lipid substitution therapy. *Skin Pharmacol. Physiol* 2015;28:42–55.
17. Trevelyan EG, Robinson N. Delphi methodology in health research: how to do it? *Eur J Integrative Med* 2015;7(4):423-428.
18. Brouwers M, Kho ME, Browman GP, et al.; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in healthcare. *Can Med Association J* 2010,182:E839-42.
19. Smith Begolka W, Elston DM, Beutner KR. American Academy of Dermatology evidence-based guideline development process: responding to new challenges and establishing transparency. *J Am Acad Dermatol.* 2011 Jun;64(6):e105-12. doi: 10.1016/j.jaad.2010.10.029.
20. Lund, CH, Osborne JW. Validity and reliability of the Neonatal Skin Condition Score. *JOGNN: J Obstet Gyn Neonatal Nurs* 2014;33(3), 320-327.
21. Schachner LA, Hansen RC. Pediatric Dermatology 4th edition December 30, 2010:952-990. eBook ISBN: 9780702062698
22. Albahrani Y, Hunt R. Newborn skincare. Pediatr Ann. 2019 Jan 1;48(1):e11-e15. doi: 10.3928/19382359-20181211-01.
23. Gregory J, Anschau N, McCutchan D, Patterson J, Martin S, Allwood M. Skincare Guidelines for babies in NICU. Kaleidoscope, *The Children's health network.* 2011
24. Younge NE, Araujo-Perez F, Brandon D, Seed PC. Early-life skin microbiota in hospitalized preterm and full-term infants. *Microbiome* 2018;6(1): 98. doi: 10.1186/s40168-018- 0486-4
25. Strugar TL, Kuo A, et al. Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier. Journal of drugs in dermatology. *J Drugs Dermatol* 2019;18(6):581.
26. Rawlings AV. Molecular basis for stratum corneum maturation and moisturization. *Br J Dermatol* 2014;171(Suppl 3):19-28
27. Chittock J, Cooke A, Lavender T, et al. development of stratum corneum chymotrypsin-like protease activity and natural moisturizing factors from birth to 4 weeks of age compared with adults. *Br J Dermatol* 2016;175(3):713-720.
28. Tessema EN, Gebre-Mariam T. Neubert RHH, Wohlrab J. Potential applications of phyto-derived ceramides in improving epidermal barrier function. *Skin Pharmacol Physiol* 2017;30:115-138. https://doi.org/10.1159/000464337
29. Meckfessel MH, Brandt S. The structure, function, and importance of ceramides in skin and their use as therapeutic agents in skincare products.

J Am Acad Dermatol 2014;71(1):177-184.
30. t'Kindt R, Jorge L, Dumont E, Couturon P, David F, Sandra P, Sandra K: Profiling and characterizing skin ceramides using reversed phase liquid chromatography-quadrupole time-of-flight mass spectrometry. *Anal Chem* 2012;84:403–411.
31. Robinson DT, Martin CR. Fatty acid requirements from the preterm infant. *Sem Fetal Neonat Med.* 2017;22:8-14.
32. Kelleher M, Dunn-Galvin A, Hourihane JO et al. Skin barrier dysfunction measured by transepidermal water loss at 2 days and 2 months predates and predicts atopic dermatitis at 1 year. *J Allergy Clin Immunol* 2015;135:930–935.
33. Lavender T, Bedwell C, Roberts SA et al (2013) Randomized, controlled trial evaluating a baby wash product on skin barrier function in healthy, term neonates. *J Obstet Gynecol Neonatal Nurs* 2013;42(2): 203-14.
34. Cooke A, Bedwell C, Campell M et al. Skin care for healthy babies at term: A systematic review of the evidence. *Midwifery.* 2018;56(1):29-43. doi: 10.1016/j.midw.2017.10.001.
35. Blume-Peytavi U, Cork MJ, Faergemann J, Szczapa J, Vanaclocha F, Gelmetti C. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *J Eur Acad Dermatol Venereol* 2009;23(7):751-9.
36. Crozier K, Macdonald S. Effective skincare regimes for term newborn infants: a structured literature review. Evidence Based Midwifery 2010;8(4):128–35.
37. Garcia Bartels N, Scheufele R, Prosch F et al. Effect of standardized skin care regimens on neonatal skin barrier function in different body areas. *Pediatr Dermatol* 2010;27(1):1-8.
38. Walters RM, Guangu M, Hornby S, et al. Cleansing formulations that respect skin barrier integrity. *Dermatol Res Pract* 2012;2012;495917. doi:10.1155/2012/495917
39. Mack MC, Chu MR, Tierney NK, Water-holding and transport properties of skin stratum corneum of infants and toddlers are different from those of adults: studies in three geographical regions and four ethnic groups," *Pediatric Dermatol* 2016;33(3):275–282.
40. Yuan C, Zou Y, Xueqiu Y, et al. Properties of skin in Chinese infants: Developmental changes in ceramides and in protein secondary structure of the stratum corneum. *BioMed Research Inter* 2017:1-6. ID 3594629
41. Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. Clinical insights about the role of skin pH in inflammatory dermatological conditions. *J Drugs Dermatol* 2019;18(12)S-1:1-16.
42. Kircik LH, Del Rosso JQ. Nonsteroidal treatment of atopic dermatitis in pediatric patients with a ceramide-dominant topical emulsion formulated with an optimized ratio of physiological lipids. *J Clin Aesthet Dermatol* 2011;4(12):25-31.
43. Lynde CW, Andriessen A. A cohort study on a ceramide-containing cleanser and moisturizer used for atopic dermatitis. *Cutis* 2014;93(4)207-2013.
44. Brandon D. Evidence based clinical practice guideline neonatal skin care - fourth edition. *AWHONN* 2018; ISBN (Print), 978-1-938299-41-4.
45. Clemison J, McGuire W. Topical emollient for preventing infection in preterm infants (review). *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD001150. DOI: 10.1002/14651858.CD001150.pub3.
46. Boull CL, Hook KP. Neonatal erythroderma – clinical perspectives. *Research Rep Neonat.* 2017;7(6):1-9.
47. WHO Recommendations on Postnatal Care of the Mother and Newborn [Internet]. Geneva, Switzerland: WHO Press; 2014.
48. Paller AS. Hurwitz's clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence. 4th ed. Atlanta: Elsevier. 2011;1-632. eBook ISBN: 9781455706860
49. Gras-Le Guen C, Caille A, Launay E, et al. Dry care versus antiseptics for umbilical cord care: a cluster randomized trial. *Pediatrics* 2017;139: e20161857.
50. Leante Castellanos JL, Perez Munuzuri A, Ruiz Campillo CW. Recommendations for the care of the umbilical cord in the newborn. *An Ped* 2019;90(6):401.el-401.e5.
51. Schachner LA, Lynde CW, Hebert AA, et al. Treatment of impetigo and antimicrobial resistence. *J Drugs Dermatol.* 2021;20(4):244-250.

AUTHOR CORRESPONDENCE

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

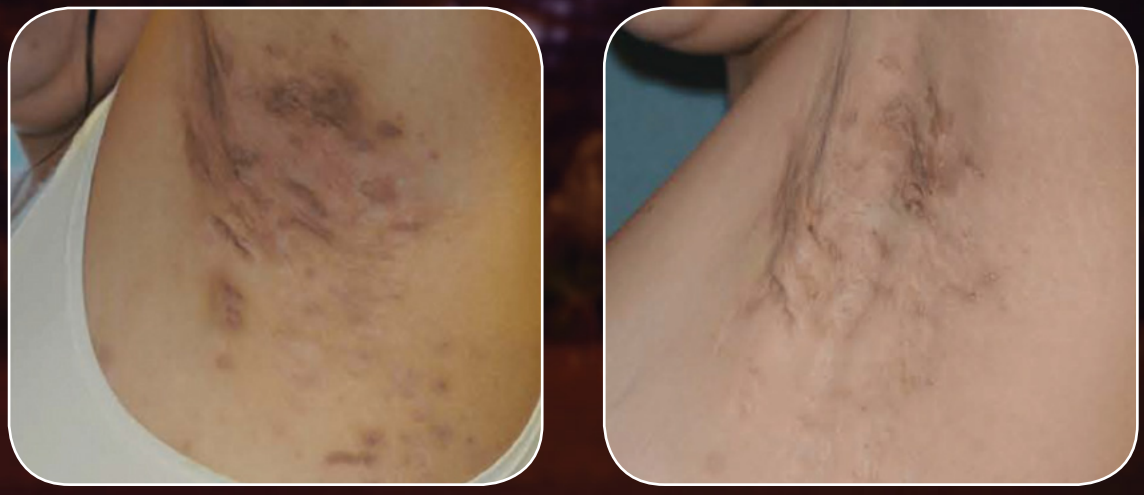
For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older

HUMIRA is the only FDA-approved treatment for your HS patients[1-3]

Results Your HS Patients Can See

MODERATE/STAGE II

Actual HUMIRA-treated patient achieving HiSCR



Before | After

Photos courtesy of Dr. Marc Bourcier

HiSCR is at least a 50% reduction in total abscess and inflammatory nodule count, with no increase in abscesses and draining fistulas relative to baseline[1]

Indication[1]

Hidradenitis Suppurativa: HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

Safety Considerations[1]

Serious Infections: Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

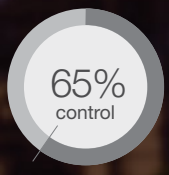
Clinically Meaningful Improvement (HiSCR) at Week 12

- In the PIONEER clinical trials, **42%** (PIONEER I) and **59%** (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR at Week 12 **(primary endpoint)**, vs **26%** and **28%** on placebo, respectively[4]

HUMIRA also has flare data available for HS

OCCURRENCE OF FLARE THROUGH 3 MONTHS[5]
Pre-specified Other Secondary Endpoint in Period A

HUMIRA-treated patients
n=316 for HUMIRA EW



Control patients
n=317 for control

PIONEER I (N=307) and II (N=326) were 36-week, randomized, double-blind, placebo-controlled clinical trials in adult patients with moderate to severe HS on HUMIRA 40-mg weekly (after initial doses).

22% (of 100) patients who were withdrawn from HUMIRA after 12 weeks experienced flare.[1,4]

PIONEER I control=placebo.
PIONEER II control=placebo +/- antibiotic.

Integrated analysis of PIONEER I and PIONEER II through 12 weeks

Flare: ≥25% increase in AN count and an absolute increase of ≥2 relative to baseline[1,5]

DATA LIMITATIONS

- **Since PIONEER I did not reach statistical significance at the first key secondary endpoint, all endpoints in this integrated analysis cannot be regarded as statistically significant**[4,5]

Safety Considerations[1] (cont'd)

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the third page of this advertisement.

Please see Brief Summary of full Prescribing Information on the pages following this advertisement.

abbvie

To learn more, please go to
ResultsforHS.com

HUMIRA®
adalimumab

IMPORTANT SAFETY INFORMATION for HUMIRA® (adalimumab)[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue HUMIRA if a patient develops a serious infection or sepsis. Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening and new onset congestive heart failure (CHF) has been reported with TNF blockers. Cases of worsening CHF have been observed with HUMIRA; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

References: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc. **2.** US Food and Drug Administration. HUMIRA approval letter for hidradenitis suppurativa. September 2015. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125057Orig1s393ltr.pdf. Published September 9, 2015. Accessed January 31, 2020. **3.** AbbVie's HUMIRA® (adalimumab) receives first and only U.S. Food and Drug Administration approval for moderate to severe hidradenitis suppurativa [press release]. North Chicago, IL: AbbVie Inc.; September 10, 2015. https://news.abbvie.com/news/abbvies-humira-adalimumab-receives-first-and-only-us-food-and-drug-administration-approval-for-moderate-to-severe-hidradenitis-suppurativa.htm. Accessed January 30, 2020. **4.** Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422-434. **5.** van der Zee HH, Longcore M, Geng Z, Garg A. Weekly adalimumab treatment decreased disease flare in hidradenitis suppurativa over 36 weeks: integrated results from the phase 3 PIONEER trials. *J Eur Acad Dermatol Venereol.* 2019 Oct 20.doi: 10.1111/jdv.16023.

abbvie

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

HUMIRA®
adalimumab

©2021 AbbVie Inc. North Chicago, IL 60064 US-HUMD-210048 March 2021 Printed in U.S.A.

HUMIRA® (adalimumab) Injection, for subcutaneous use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn's Disease

HUMIRA is indicated for the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

Ulcerative Colitis

HUMIRA is indicated for the treatment of moderately to severely active ulcerative colitis in adults and pediatric patients 5 years of age and older.

Limitations of Use

The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients 65 years of age and older, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps), hidradenitis suppurativa (HS) and uveitis (UV), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA, hypersensitivity reactions (e.g., rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Increased Risk of Infection when Used with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Increased Risk of Infection When Used with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Hepatitis B Virus Reactivation *[see Warnings and Precautions]*
- Neurologic Reactions *[see Warnings and Precautions]*
- Hematological Reactions *[see Warnings and Precautions]*
- Heart Failure *[see Warnings and Precautions]*
- Autoimmunity *[see Warnings and Precautions]*

Clinical Trials Experience

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

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with Crohn's Disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in adult patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In the controlled Phase 3 trial of HUMIRA in patients with pediatric ulcerative colitis (N=93), which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight based induction doses of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in adult patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions, Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK concentrations decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies

Adults: The safety profile of HUMIRA in 1478 adult patients with Crohn's disease from four placebo-controlled and two open-label extension studies was similar to the safety profile seen in patients with RA.

Pediatric Patients 6 Years to 17 Years: The safety profile of HUMIRA in 192 pediatric patients from one double-blind study (Study PCD-I) and one open-label extension study was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4-week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis. In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

Adults: The safety profile of HUMIRA in 1010 adult patients with ulcerative colitis (UC) from two placebo-controlled studies and one open-label extension study was similar to the safety profile seen in patients with RA.

Pediatric Patients 5 Years to 17 Years: The safety profile of HUMIRA in 93 pediatric patients with ulcerative colitis from one double-blind study and one open-label extension study was similar to the safety profile seen in adult patients with ulcerative colitis.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 adult patients with uveitis (UV) in placebo-controlled and open-label extension studies and in 90 pediatric patients with uveitis (Study PUV-I). The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Immunogenicity

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

There are two assays that have been used to measure anti-adalimumab antibodies. With the ELISA, antibodies to adalimumab could be detected only when serum adalimumab concentrations were < 2 mcg/mL. The ECL assay can detect anti-adalimumab antibody titers independent of adalimumab concentrations in the serum samples. The incidence of anti-adalimumab antibody (AAA) development in patients treated with HUMIRA are presented in Table 2.

Table 2: Anti-Adalimumab Antibody Development Determined by ELISA and ECL Assay in Patients Treated with HUMIRA

Indications		Study Duration	Anti-Adalimumab Antibody Incidence by ELISA (n/N)		Anti-Adalimumab Antibody Incidence by ECL Assay (n/N)
			In all patients who received adalimumab	In patients with serum adalimumab concentrations < 2 mcg/mL	
Rheumatoid Arthritis[a]		6 to 12 months	5% (58/1062)	NR	NA
Juvenile Idiopathic Arthritis (JIA)	4 to 17 years of age[b]	48 weeks	16% (27/171)	NR	NA
	2 to 4 years of age or ≥ 4 years of age and weighing < 15 kg	24 weeks	7% (1/15)[c]	NR	NA
Psoriatic Arthritis[d]		48 weeks[e]	13% (24/178)	NR	NA
Ankylosing Spondylitis		24 weeks	9% (16/185)	NR	NA
Adult Crohn's Disease		56 weeks	3% (7/269)	8% (7/86)	NA
Pediatric Crohn's Disease		52 weeks	3% (6/182)	10% (6/58)	NA
Adult Ulcerative Colitis		52 weeks	5% (19/360)	21% (19/92)	NA
Pediatric Ulcerative Colitis		52 weeks	3% (3/100)	13% (3/23)	33% (33/100)[i]
Plaque Psoriasis[f]		Up to 52 weeks[g]	8% (77/920)	21% (77/372)	NA
Hidradenitis Suppurativa		36 weeks	7% (30/461)	28% (58/207)[h]	61% (272/445)[j]
Non-infectious Uveitis		52 weeks	5% (12/249)	21% (12/57)	40% (99/249)[k]

n: number of patients with anti-adalimumab antibody; NR: not reported; NA: Not applicable (not performed)

[a] In patients receiving concomitant methotrexate (MTX), the incidence of anti-adalimumab antibody was 1% compared to 12% with HUMIRA monotherapy

[b] In patients receiving concomitant MTX, the incidence of anti-adalimumab antibody was 6% compared to 26% with HUMIRA monotherapy

[c] This patient received concomitant MTX

[d] In patients receiving concomitant MTX, the incidence of antibody development was 7% compared to 1% in RA

[e] Subjects enrolled after completing 2 previous studies of 24 weeks or 12 weeks of treatments.

[f] In plaque psoriasis patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal

[g] One 12-week Phase 2 study and one 52-week Phase 3 study

[h] Among subjects in the 2 Phase 3 studies who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to <2 mcg/mL (approximately 22% of total subjects studied)

[i] No apparent association between antibody development and safety was observed. The association of antibody development and efficacy outcome was not assessed due to limited number of subjects in each treatment group stratified by anti-adalimumab antibody titer.

[j] No apparent association between antibody development and safety was observed

[k] No correlation of antibody development to safety or efficacy outcomes was observed

Rheumatoid Arthritis and Psoriatic Arthritis: Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab using the ELISA during the 6- to 12-month period. No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

Postmarketing Experience

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

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, lichenoid skin reaction

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been observed with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased concentrations of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby HUMIRA Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn's disease (CD). Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease-matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data)*.

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations)*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data)*.

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

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

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data)*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

In an independent clinical study conducted in ten pregnant women with IBD treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood concentration of adalimumab was higher than the maternal serum concentration, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum concentrations at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum concentration. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of HUMIRA have been established for:

- reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 2 years of age and older.
- the treatment of moderately to severely active Crohn's disease in pediatric patients 6 years of age and older.
- the treatment of moderately to severely active ulcerative colitis in pediatric patients 5 years of age and older.
- the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.
- the treatment of non-infectious intermediate, posterior, and panuveitis in pediatric patients 2 years of age and older.

Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab concentrations in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with JIA less than 2 years of age.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active Crohn's disease have been established in pediatric patients 6 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of HUMIRA in 192 pediatric patients (6 years to 17 years of age) *[see Adverse Reactions]*. The adverse reaction profile in patients 6 years to 17 years of age was similar to adults.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with Crohn's disease less than 6 years of age.

Pediatric Ulcerative Colitis

The safety and effectiveness of HUMIRA for the treatment of moderately to severely active ulcerative colitis have been established in pediatric patients 5 years of age and older. Use of HUMIRA for this indication is supported by evidence from adequate and well-controlled studies in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose concentrations of HUMIRA in 93 pediatric patients (5 years to 17 years of age) *[see Adverse Reactions]*. The adverse reaction profile in patients 5 years to 17 years of age was similar to adults.

The effectiveness of HUMIRA has not been established in patients who have lost response or were intolerant to TNF blockers.

The safety and effectiveness of HUMIRA have not been established in pediatric patients with ulcerative colitis less than 5 years of age.

Pediatric Uveitis

The safety and effectiveness of HUMIRA for the treatment of non-infectious uveitis have been established in pediatric patients 2 years of age and older. The use of HUMIRA is supported by evidence from adequate and well-controlled studies of HUMIRA in adults and a 2:1 randomized, controlled clinical study in 90 pediatric patients. The safety and effectiveness of HUMIRA have not been established in pediatric patients with uveitis less than 2 years of age.

Hidradenitis Suppurativa

Use of HUMIRA in pediatric patients 12 years of age and older for HS is supported by evidence from adequate and well-controlled studies of HUMIRA in adult HS patients. Additional population pharmacokinetic modeling and simulation predicted that weight-based dosing of HUMIRA in pediatric patients 12 years of age and older can provide generally similar exposure to adult HS patients. The course of HS is sufficiently similar in adult and adolescent patients to allow extrapolation of data from adult to adolescent patients. The recommended dosage in pediatric patients 12 years of age or older is based on body weight.

The safety and effectiveness of HUMIRA have not been established in patients less than 12 years of age with HS.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients 65 years of age and older was higher than for those less than 65 years of age. Consider the benefits and risks of HUMIRA in patients 65 years of age and older. In patients treated with HUMIRA, closely monitor for the development of infection or malignancy *[see Warnings and Precautions]*.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

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

Infections

Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections *[see Warnings and Precautions]*.

Malignancies

Counsel patients about the risk of malignancies while receiving HUMIRA *[see Warnings and Precautions]*

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity reactions. Advise latex-sensitive patients that the needle cap of the HUMIRA 40 mg/0.8 mL Pen and 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL prefilled syringe may contain natural rubber latex *[see Warnings and Precautions]*.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever *[see Warnings and Precautions]*.

AbbVie Inc.
North Chicago, IL 60064, U.S.A.
US License Number 1889
Ref: 20066565 Revised: 2/2021

LAB-4656 **MASTER**

US-HUMD-210048

abbvie

doi:10.36849/JDD.6259

November 2021 1213 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Recommendations for Using Over-the-Counter Products as Adjunctive Acne Care in Asian Phototypes: Improving Treatment Outcomes and Managing Side Effects

Anneke Andriessen PhD,[a] Xian Jiang MD PhD,[b] Kanokvalai Kulthanan MD,[c] Chih-Hung Lee MD PhD,[d] Rodney Sinclair MBBS, MD, FACD,[e] Cheng-Feng Zhang MD PhD[f]

[a]Radboud University Medical Center, Nijmegen, The Netherlands; Andriessen Consultants, Malden, The Netherlands
[b]Department of Dermatology, West China Hospital, Sichuan University, Chengdu, China; Laboratory of Dermatology, Clinical Institute of Inflammation and Immunology (CIII), Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, China
[c]Siriraj Hospital of Mahidol University, Bangkok, Thailand
[d]Department of Dermatology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[e]University of Melbourne, Victoria, Australia; Wellington Parade, East Melbourne, Australia
[f]Department of Dermatology, Huashan Hospital of Fudan University, Shanghai, China

ABSTRACT

Background: Acne vulgaris (acne) is a common inflammatory skin disorder prevalent among all ethnic groups. This review aimed to investigate the current literature regarding the potential benefit of over-the-counter (OTC) adjuncts (eg, moisturizers, cleansers) for acne patients focusing on Asian phenotypes.

Methods: An online procedure was employed to review the role of adjunctive OTC acne treatment. A panel consisting of dermatologists with expertise in treating Asian acne patients participated in a pre-meeting survey that collected information regarding their recommendation habits for OTC products in acne patients. Recommendations on using OTC products as an adjunct for treating acne in Asians are based on the pre-meeting survey results, evidence from literature presented during a series of plenary lectures, and discussions conducted during a stepwise program of sessions.

Results: Many topical treatments have been associated with adverse events (AEs) (eg, skin dryness, erythema, scaling, stinging, burning, pruritus). Multiple studies on topical acne treatments have found that Asians display greater sensitivity and less tolerability than Caucasians to acne treatment. Skincare as an adjunct to acne treatment may reduce dryness or irritation, particularly important in Asians with acne.

Conclusions: Advisors agreed that cleansers and moisturizers should be considered for their beneficial adjunctive role in the armamentarium of acne treatment and maintenance strategies.

J Drugs Dermatol. 2021;20(11):1213-1221. doi:10.36849/JDD.6259

INTRODUCTION

Acne: Etiology, Pathogenesis, Epidemiology, Quality of Life

Acne vulgaris (acne) is an inflammatory skin disorder with multifactorial etiopathogenesis. Factors including follicular epidermal hyperproliferation, sebum hyperproduction, inflammation, and colonization by *Cutibacterium acnes* are implemented in the development and/or exacerbation of acne.[1] Depending on disease severity, acne breakouts can consist of non-inflammatory (ie, open blackheads or closed comedones) and/or inflammatory lesions (ie, papules, pustules, nodules, cysts and/or macules), frequently appearing on the face but also occurring in other body regions (eg, back, chest). The Global Burden of Disease Project ranks acne as the eighth most prevalent disease worldwide,[2,3] with a global prevalence rate estimated at 9.4%. Acne most often occurs in adolescence, with incidence rates peaking between the ages of 14–17 years for females and 16-19 years for males.[4,5] This inflammatory skin disorder, however, is also becoming more prevalent among the adult population.[5,6] Being a distressing disorder, acne negatively affects the quality of life and psychosocial wellbeing (eg, anxiety, depression, low self-esteem). Acne can also lead to physical complications, such as permanent scarring.[7,8]

Acne: Prescription Treatments

The choice of prescription treatment for acne depends strongly on the type (inflammatory versus non-inflammatory), underlying causes (eg, polycystic ovarian syndrome), and

severity of lesions. Systemic (eg, antibiotics, hormone therapy) and topical (eg, isotretinoin gel, benzoyl peroxide, salicylic acid) prescription medications are available as monotherapies or combination treatments. The "Global Alliance to Improve Outcomes in Acne" recommends using combination agents to target most of the pathophysiological features of acne, not only as they can target multiple processes, but they can also provide faster and more complete lesion clearance compared to monotherapy.[9] Unfortunately, topical treatments have been associated with side effects, including visible signs of intolerance such as skin dryness, erythema, and scaling, as well as subjective symptoms of irritation such as stinging, burning, and itching. Studies reveal that experiencing side effects can reduce adherence to acne treatment by up to 50%,[10] with non-use of moisturizing creams and cleansers also being linked to poor compliance.[11]

Acne: Non-Prescription Adjuvants

Over-the-counter (OTC) products play a primarily adjunctive role in acne treatment and maintenance. Relevant OTC products may include skin cleansers, moisturizers, and sunscreens, among others. These products may offer several benefits to acne-prone skin, such as reducing oiliness, redness, inflammation, pain/discomfort, improving skin texture, time for lesions to heal, the extent of scarring, and potentially, the number and severity of acne breakouts.[12] They may provide adjunctive benefits, such as helping to treat the signs and symptoms of acne, and/or they may play a role in acne maintenance by mitigating side effects of prescription medications, thereby improving treatment compliance and outcomes.[13,14] Notably, the market for OTC acne products is an order of magnitude larger than that for prescription medications, and acne patients commonly use homeopathy.[15] As many acne patients have been reported to try multiple OTC products prior to seeking medical attention and often continue using them while receiving prescription therapy; OTC products may impact treatment outcomes.

Acne in Asian-Pacific Skin

In the 21st century, there was an important demographic change, with half of the world's population identifying as "Asian"; a term generally referring to those from the Asian-Pacific (APAC) regions of East, South, and Southeast Asia, and can include Oceania and/or the Indian subcontinent. Partially due to this population growth, Asians also make up one of the fastest-growing ethnic groups desiring aesthetic treatments and procedures.[16] Other factors contributing to this trend include increasing disposable income and shifts in social perceptions of acceptability regarding aesthetics.[2,5,6] Given their differential skin characteristics (eg, melanin content), specific environmental/geographical factors (eg, pollution), and unique cultural (eg, diet) and psychosocial influences, Asians represent a distinct ethnic group. Among Chinese and Japanese subjects, Asian skin typically consists of Fitzpatrick phenotypes III to IV (light to moderate brown), while types IV and V (dark brown) is more common among Indians and Pakistanis.[17] Therefore, Asian skin tends to consist of more melanin than their Caucasian counterparts (Fitzpatrick types I to III), allowing for superior natural photoprotection while also increasing the risk of pigmentary disorders. Post-inflammatory hyperpigmentation is peculiar to this skin type, which can occur after cutaneous damage from acne lesions or following the use of laser therapy. The treatment-seeking behaviors and related epidemiological features in Asian acne patients have been found to vary from that of the rest of the world,[18] and multiple studies on topical acne treatments have found that Asians display greater sensitivity and less tolerability than Caucasians.[19] For example, approximately 80% of Japanese patients experienced mild adverse effects following the first month of adapalene use, compared to the 20–30% observed in trials involving Caucasians.[15]

Currently, there is limited data regarding the use of OTC adjuvants in acne treatment and maintenance, and trends in clinical practice are not consistent in this regard. Moreover, it is important to continue studying the unique challenges of treating acne in Asian skin, to optimize clinical outcomes in this population.[2,5,6,17] The current manuscript aimed to evaluate the role of OTC products in the treatment of acne, particularly in Asian skin.

MATERIALS AND METHODS

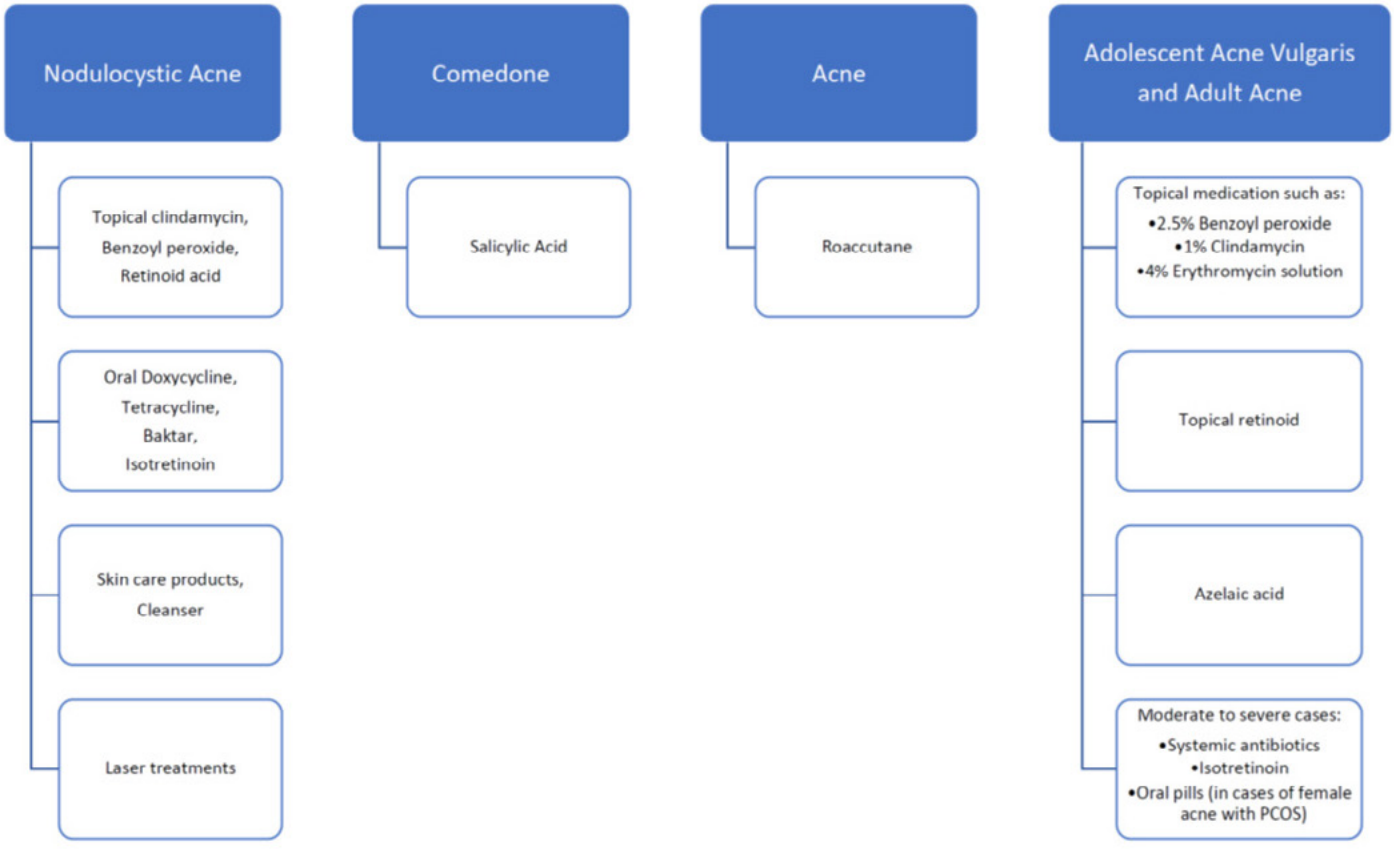
An advisory panel consisting of key opinion leaders and dermatologists with expertise in the treatment and maintenance of acne in Asian skin was held in December 2020, via web conference. Prior to the meeting, advisors participated in an online survey that collected data regarding: which (if any) OTC products they currently recommend for acne patients; for which (if any) patient profiles do they recommend these products; when they recommend OTC adjunctive therapies be used; how they recommend OTC products be used; and why advisors recommend specific OTC products as adjuncts to acne therapy. The pre-meeting survey results, evidence from the literature presented during a series of plenary lectures, and discussions conducted during a stepwise program of sessions were used to develop recommendations on the use of OTC products as an adjunct for treating acne in Asians.

RESULTS

Survey

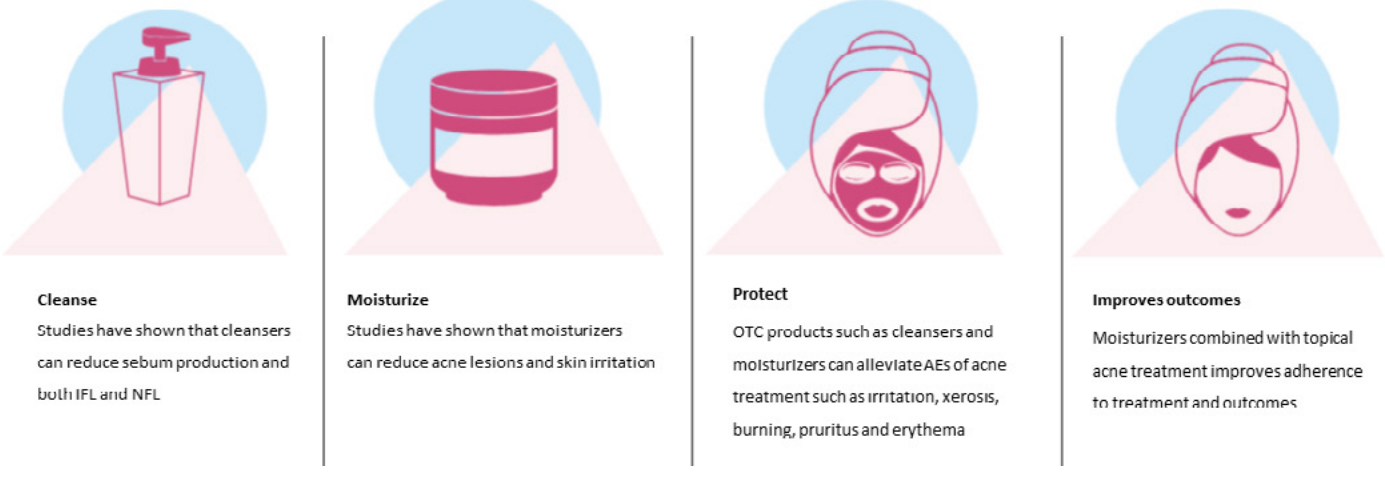
Acne subtypes observed in the clinics of advisors and the corresponding therapeutic option(s) used to treat these conditions are displayed in Figure 1. According to advisors, OTC products currently serve an adjunctive role under three main conditions: 1) used remedially prior to or in combination with prescription medications, 2) post-procedural use (eg, after a chemical peel, microdermabrasion, laser therapy), or 3) when used as part of a maintenance regimen. Advisors reported

FIGURE 1. Acne subtypes observed in the clinics of advisors and the corresponding therapeutic option(s) used to treat these conditions.



Polycystic ovary syndrome (PCOS)

FIGURE 2. Summary of the benefits of OTC products as adjuncts to acne treatment for patients with acne-prone skin.



Over-the-counter (OTC), Inflammatory lesions (IFL), Non-inflammatory lesions (NFL), Adverse events (AEs)

TABLE 1.

What Is Your Choice of OTC Product for Acne Monotherapy?

No.	Authors	Title	Study design	Endpoint(s) of interest	Conclusions regarding OTC products for acne-prone skin
1	Angelova-Fischer I, et al. J Eur Acad Dermatol Venereol. 2013;27:6–11.13	A double-blind, randomized, vehicle-controlled efficacy assessment study of a skin care formulation for improvement of mild to moderately severe acne	A double-blind, randomized, vehicle-controlled study to assess the stand-alone efficacy of a skin care formulation in 60 volunteers with mild to moderately severe acne. Subjects were randomized into two groups (active formulation versus vehicle) twice daily, for 8 weeks	After 8 weeks, the active formulation group showed a reduction in the mean total lesion count, papules, pustules, sebum levels and P. acnes colonization	The application of a moisturizer improves acne treatment outcomes, compared to vehicle
2	Abad-Casintahan F, et al. J Derm. 2011;38(11):1041-1048.15	Toward evidence-based practice in acne: consensus of an Asian working group	Experts from ten countries reviewed acne care within the APAC region	An algorithm for acne care, based on the results of clinical trials and local practice patterns	Physicians and other care providers should be educated on non-pharmalogical options for effective acne therapy
3	Choi JM, et al. Pediatr Dermatol. 2006;23:421–7.20	A single-blinded, randomized, controlled clinical trial evaluating the effect of face washing on acne vulgaris	Randomized clinical trial	Effect of face washing on acne	Washing twice daily improves both open comedones and total noninflammatory lesions
4	Choi YS, et al. J Dermatol Treat 2010;21:201–5.21	A study of the efficacy of cleansers for acne vulgaris	Eight-week, double-blind, randomized clinical trial in 13 acne patients	Effectiveness of cleansers to produce clinical improvements in acne	Cleansers reduced both inflammatory and non-inflammatory lesions and may be helpful for acne treatment
5	Dreno B, et al. J Eur Acad Dermatol Venereol. 2013;27: 1071–80.22	Algorithm for dermocosmetic use in the management of cutaneous side-effects associated with targeted therapy in oncology	Review of published experimental vehicle systems for benzoyl peroxide	Identify formulations that can improve the tolerability of benzoyl peroxide	An increase in tolerability to benzoyl peroxide can be achieved by combining it with moisturizing substances
6	Goh CL, et al. J Cut Aesthet Surg. 2016;9(2):85-92.23	Meeting the challenges of acne treatment in Asian patients: a review of the role of dermocosmetics as adjunctive therapy	Review of the evidence on dermocosmetics use in APAC acne populations	Practice recommendations on the role of dermocosmetics as adjunct for treating acne in Asian patients	Appropriate use of dermocosmetics may help augment the benefits of acne treatment, minimize side effects, and reduce the need for topical antibiotics
7	Chularojanamontri L, et al. J Dermatol Treat. 2016;27(2):140-145. 26	A double-blinded, randomized, vehicle-controlled study to access skin tolerability and efficacy of an anti-inflammatory moisturizer in treatment of acne with 0.1% adapalene gel	Randomized clinical study in 120 subjects	Cutaneous irritations to acne medications	The combined use of adapalene gel and moisturizer can reduce undesirable side effects without interfering the efficacy of adapalene
8	Lynde CW,et al. J Drugs Dermatol. 2019 Dec 1;18(12):221.28	Clinical Insights About the Role of pH in Acne	Consensus recommendations	Explore the influence of skin pH on acne	As an adjunct to treatment, a pH-balanced ceramide containing cleanser and moisturizer may help in managing skin barrier function
9	Lain E, Andriessen AE J Drugs Dermatol. 2020 Nov 19(11):217.29	Choosing the right partner: Complementing prescription acne medication with over-the-counter cleansers and moisturizers	Literature review	Explore the importance of adjunctive skincare for managing acne and avoiding adverse events	Adjunctive skincare may complement prescription therapy and benefit skin barrier dysfunction

TABLE 1. (CONTINUED)

What Is Your Choice of OTC Product for Acne Monotherapy?					
No.	**Authors**	**Title**	**Study design**	**Endpoint(s) of interest**	**Conclusions regarding OTC products for acne-prone skin**
10	Munehiro A, et al. J Dermatol Treat. 2012 Jun; 23(3):172-6.33	Combination effects of cosmetic moisturizers in the topical treatment of acne vulgaris	Cohort of 18 male Japanese patients with acne vulgaris who were treated with the topical administration of adapalene and clindamycin phosphate gels, plus moisturizers	The use of moisturizers did not impact the efficacy of the standard topical acne treatment and they significantly improved the water content of the stratum corneum and the sensation of dryness.	Using moisturizers in combination with standard topical acne treatments may improve adherence to therapy by alleviating the sensation of dryness.
11	Hayashi N, Kawashima M. J Dermatol Treat. 2012 Jun; 23(3):172-6.34	Study of the usefulness of moisturizers on adherence of acne patients treated with adapalene.	100 patients with acne vulgaris were randomly assigned to one of two groups: group A (adapalene + moisturizer) or group B (adapalene alone). Adherence to treatment was assessed after 4 weeks of treatment.	Examine the usefulness of moisturizers concomitant with adapalene on adherence to treatment and its therapeutic effects.	The concomitant use of a moisturizer with adapalene did not affect its therapeutic effects and helped to improve adherence to treatment with adapalene.
12	Matsunaga K, et al. J Dermatol Treat. 2013 Aug; 24(4):278-82.35	Adjunctive usage of a non-comedogenic moisturizer with adapalene gel 0.1% improves local tolerance: a randomized, investigator-blinded, split-face study in healthy Asian subjects	Four-week, randomized, investigator-blinded, split-face study among 30 healthy volunteers of Chinese origin. Adapalene gel was applied once daily to the whole face and a moisturizing lotion was applied once daily to only one side of the face according to the randomization scheme.	Investigator and subject reported tolerance (erythema, desquamation, dryness, stinging/burning and pruritus)	The adjunctive usage of an effective moisturizer improves local tolerance of adapalene gel and may contribute to better adherence
13	Chularojanamontri L, et al. J Clin Aesthet Dermatol. 2014 May; 7(5):36-44.36	Moisturizers for Acne: What are their Constituents?	A review of the active ingredients and properties of moisturizers suitable for acne-prone skin	Most products had anti-inflammatory, occlusive, humectant, and emollient properties	Scientific data regarding available ingredients are discussed to guide physicians in selecting moisturizers for acne patients
14	Bikowski J Cutis. 2001 Dec; 68(5 Suppl):3-11.37	The use of therapeutic moisturizers in various dermatologic disorders	Narrative review	Role of moisturizers as adjuncts to acne therapy	Moisturizers can serve as important adjunctive therapeutic modalities for patients with various dermatologic disorders, including acne vulgaris
15	Angelova-Fischer I, et al. J Cosmet Dermatol. 2012;11:30–6.38	Topically applied L-carnitine effectively reduces sebum secretion in human skin	A three-week, vehicle-controlled, randomized, clinical trial	Sebum production	Topically applied moisturizers can lead to significant sebum reduction in subjects with oily skin
16	Andriessen A, et al. J Drugs Dermatol. 2021 Mar 1;20(3):244-250.	Over the Counter Products for Acne Treatment and Maintenance in Latin America: A Review of Current Clinical Practice	Survey of clinical practice and literature review	Investigate real-world OTC product recommendations for acne patients	Advising dermatologists agreed that OTC products used as adjuncts are a crucial part of a successful acne therapy and can improve acne symptomology and severity

N = 5 Once a day (QD), Twice a day (BID), Not specified (ns)

TABLE 2.

What Is Your Choice of OTC Product for Acne Adjunct Therapy?					
Choice	**Product Name**	**Where would you use this product?**	**When would you use this product?**	**How would you use this product?**	**Why would you use this product?**
First	Differin, Galderma	Comedones and scars	Every night	QD	Normalization of keratinization
	Avene Diacneal	ns	ns	ns	ns
	Benzac Wash	Face, back, chest	ns	QD before shower	Prophylaxis against relapse or mild popular disease
	Effaclar Duo plus	On the face	When acne lesions subside and leave post acne redness and hyperpigmentation	QD or BID	Because patients always concern of the residual of acne lesions
	SkinCeuticals	Face	Local treatment Mild acne	BID	Good effect
Second	Duac, GSK-Stiefel	Inflamed cysts and nodules with comedones	Facial inflamed skin lesions	QD to BID	Combination of BP and Clindamycin
	Clindatech	Face	ns	QD	Pustules
	Eucerin Proacne solution	Face, sometimes trunk	In the maintenance phase of acne	QD or BID	It contain salicylic acid, lichocalcone (antiinflammatory property), L-carnitine (control sebum), Decanidiol (decrease acne biofilm formation)
Third	Skinoren, azelaic acid, Bayer	Pigmentations and scars with minimal inflammation	Facial lesions	BID	Normalization of keratinization and pigmentation
	Neutrogena facial foam scrub	On face	To clean the face in patients who have seborrhea	BID	In mild cases, to clear mild comedonal lesions

N = 5 Once a day (QD), Twice a day (BID), Not specified (ns)

TABLE 3.

What Is Your Choice of OTC Product for Acne Maintenance Therapy?					
Choice	**Product Name**	**Where would you use this product?**	**When would you use this product?**	**How would you use this product?**	**Why would you use this product?**
First	Neutrogena cleanser	Greasy facial skin	Facial cleansing	BID	Patient compliance and consistency
	CeraVe Foaming Cleanser	Face, trunk	Cleanser	BID	Gentle cleanser
	Cetaphil cleanser	Face	Cleanser	BID	Make-up removal
	Effaclar Duo	Face, trunk	When acne lesions subside and leave post acne redness and hyperpigmentation	BID	Because patients are always concerned about post inflammatory hyperpigmentation and redness
	Effaclar Mild regime, La Roche-Posay	Face	Before and after drug treatment	QD	Adjuvant therapy, clean and moisturizing
Second	Effaclar, La Roche Posay	Greasy skin with mild erythema	Cleansing	BID	Compliance and consistency
	CeraVe cream	Face	In patients who have dry skin when using topical antiacne preparation and those who receive oral isotretinoin	Apply on the whole face	Pustules
	QD or BID	To increase patients' compliance	In the maintenance phase of acne	QD or BID	It contain salicylic acid, lichocalcone (antiinflammatory property), L-carnitine (control sebum), Decanidiol (decrease acne biofilm formation)
Third	Curél intensive moisturizing cream	Greasy skin with moderate inflammation	ns	BID	Light, consistency, and Asian skin
	Eucerin Proacne solution	Face, sometimes trunk	Face, sometimes trunk	QD or BID	It contain salicylic acid, lichocalcone (antiinflammatory property), L-carnitine (control sebum), Decanidiol (decrease acne biofilm formation)

N = 5 Once a day (QD), Twice a day (BID), Not specified (ns)

TABLE 4.

Literature Regarding the Use of OTC Products in Patients With Acne-Prone Skin

Choice	Product Name	Where would you use this product?	When would you use this product?	How would you use this product?	Why would you use this product?
First	CeraVe acne foaming	Residual inflammation and minimal scars	Cleansing	QD	Good cleansing effects with antimicrobiome and keratinization normalization
	Eucerin Proacne solution	Face, sometimes trunk	When lesions subside for more than 50% of the baseline	BID	It contain salicylic acid, lichocalcone (antiinflammatory property), L-carnitine (control sebum), Decanidiol (decrease acne biofilm formation)
	SkinCeuticals	Face	Before and after drug	If needed	Adjuvant and maintenace therapy
Second	Cetaphil	Minimal inflammations and comedones	Cleansing	QD	Good compliance
	AcneAid liquid cleanser or bar	Face or trunk	As cleansers	BID	They contained salicylic acid which help to prevent new acne lesions
	LRP	Face	Before and after drug	If needed	Adjuvant and maintenance therapy
Third	SK-II	With some pigmentations	ns	QD	AHA, Asian, and consistency
	CeraVe acne foaming cream cleanser	Face, trunk	When acne lesions subside	BID	It contains benzyol peroxide which is effective in treating acne lesions and also contains niacinamide which help reducing inflammation.

N = 5 Once a day (QD), Twice a day (BID), Not specified (ns)

recommending OTC products also when encouraging the use of a photoprotective product that is still suitable for acne-prone skin (ie, non-greasy formulation, thin application). When asked what advisors looked for in an OTC adjunct to acne therapy, responses included being physiological-based, hypoallergenic, affordable, and able to provide long-lasting moisturization. To reduce unwanted side effects of prescription acne treatments (eg, drying, stinging), the panel recommended that moisturizers be applied prior to other topical agents.

Product recommendations varied depending on the primary intended use of the products (ie, as a stand-alone therapy; as an adjunct to treatment; for maintenance of treatment results). For acne monotherapy, OTC products reported to be used by advisors included SkinCeuticals, Effaclar Duo+, Benzac Wash, Avène Diacneal, and Differin (Table 1). Adjunctive and maintenance OTC products included La Roche Posay, Effaclar Duo Plus, Cetaphil, CeraVe Foaming Cleanser, and Neutrogena cleanser (Table 2 and Table 3).

For cleansers, advisors stressed the caveat that Asian skin tends to be more sensitive than other phototypes. Thus, irritants commonly included in cleansers for acne-prone skin (eg, salicylic acid) may lead to greater severities of irritation in these patients. Concentrations of these ingredients may need to be lower in products aimed at targeting the Asian market, or less irritating ingredients should be considered. For example, advisors proposed using 10–15% azelaic acid instead of 2% salicylic acid in a product targeting pigmentation. It was also thought useful to add ingredients capable of counteracting the transient irritation caused by azelaic acid. Other ingredients found suitable by the advisors were nicotinic acid and/or tranexamic acid. Advisors concluded that there is a current unmet need for an economical product indicated for face, back, and chest acne and that the ideal product to be used in an acne regimen would include lipid-free cleansers, synthetic detergents (syndets), astringents, exfoliants, or mild abrasives. Cleansing liquids were preferred over bars. Finally, the expert panel concluded that, while the choice of the cleanser should be suited to the patient's skin profile, all acne patients can benefit from a cleansing regimen and should therefore be educated on the proper selection and use of cleansers, as they have been found to increase treatment compliance and reduce lesions.[20,21]

DISCUSSION

Supporting Literature

A list of literature regarding the use of OTC products in acne-prone skin is displayed in Table 4. A recent large-scale review of a national patient database revealed that acne monotherapies are typically prescribed without co-prescribing topical non-antibiotic agents.[12] However, OTC products are believed to target various etiopathogenic factors of acne (eg, antibacterial,

anti-inflammatory, reductant of sebum, dryness, irritation), may improve the penetration of prescribed topical medications, or may help mitigate side effects of treatments.[22] Appropriate use of OTC products may help improve the effectiveness of acne treatment, minimize side effects, and reduce the need for topical antibiotics. This is of growing importance in a world where *C. acnes* resistance progresses at an alarming rate due to continued antibiotic use.[4]The need for alternative, non-antibiotic treatments for acne is now widely accepted.[5]

Several groups have produced independent acne treatment guidelines, but few have previously considered practices specific to the APAC region. A group of global experts, including from nine Asian countries and the United States, have previously gathered to review clinical trial data and local practice patterns. This resulted in the development of a best practice algorithm and recommendations for the treatment of acne in Asian patients.[15] The experts concluded that physicians and other care providers should be educated on non-pharmacological options for effective acne therapy.

In 2015, twenty-one Asian dermatologists from Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, Vietnam, and Italy met to discuss and provide insight into current treatment practices in acne therapy and OTC product recommendations. The advisors reviewed the perspectives of dermatologists from different centers around APAC that regularly treat acne patients and achieved a general consensus that OTC agents can target various etiopathogenic factors relevant to acne.[23]This may include antibacterial and anti-inflammatory properties, reduction of sebum, dryness, irritation, photosensitivity, and enhancing the penetration of prescribed topical medications.[22] Most of the OTC products reviewed by the experts were found to include components that target inflammation, wound healing, photoaging, hyperpigmentation, or uneven skin texture.[23]

Recent advances in understanding normal skin physiology and the pathophysiology of acne should allow for the development of OTC therapies capable of offering a broad spectrum of treatment targets.[6,24] For example, OTC products can now be manufactured in such a way as to make them especially suitable as an acne treatment/monotherapy or an adjunct to mitigate side effects of another treatment. Previous studies have found that moisturizers can improve disease severity in patients with mild-to-moderate acne,[13,25] and that a greater reduction in lesion counts, papules, pustules, *C. acnes* colonization, and sebum production is observed after eight weeks of adjunctive use, compare to treatment alone.[26] Since there is an overwhelming amount of OTC products available, clinicians should be well-equipped with the knowledge base to advise patients on the products best suitable for their skin.

Future Directions

Product development

There is a need to consider the unique characteristics of acne-prone Asian skin to identify better therapeutic strategies, management techniques and improve clinical outcomes.[17] OTC acne products targeting Asian skin should be suitable for sensitive skin, susceptible to post-inflammatory hyperpigmentation. Moreover, given the skin barrier disruptions observed in acne, there may be unique benefits of ceramide-containing cleansers and moisturizers for patients with this chronic, relapsing disorder.[27] OTC products targeted for acne-prone skin should also promote the maintenance of an acidic skin surface, which may help to ensure skin barrier integrity and reduce dry, irritated skin.[28,29] This can be achieved by the product being compatible with a pH of 4 to 5.

Education

Physicians and patients should be educated on the varied uses of OTC products for acne-prone skin (Figure 2). Educating physicians may encourage them to recommend these products to patients being prescribed acne treatments known to be topically irritating to help mitigate side effects, improve treatment compliance, and improve the effectiveness of prescription medications. Conversely, efforts to directly educate the general population on the proper use of adjunctive OTC acne care may be particularly important, as many acne sufferers self-manage their condition and do not consult with clinicians.[30,31] For example, a study on treatment-seeking behaviors showed that most Korean patients primarily sought skin care advice from different media outlets; and had a tendency to favor traditional medicine methods. Moreover, as acne treatment in Asia comes from various providers [e.g., dermatologists, primary care physicians, non-healthcare personnel (beauticians)], publishing recommendations for managing Asian patients with acne can be helpful to many professionals offering aesthetic and cosmetic care.[15] In fact, in many Asian countries, the proportion of dermatologists to the overall population is low; therefore, most patients are not managed by specialists. A survey of 200 participants revealed that 41% of acne sufferers use a moisturizer to cope with the unwanted side effects of their topical acne treatments.[32] Therefore, there are many non-medical care providers and patients that would benefit from the guidance of dermatologists regarding the armamentarium of OTC products.[15]

LIMITATIONS

Asians represent extensive populations that are not well defined. Relationships between age, skin type, geographical area, specific acne symptoms, skincare, and acne treatment are not extensively studied.

CONCLUSION

The advisors agreed that OTC products, such as cleansers and

moisturizers, should be considered for their adjunctive role in the armamentarium of acne treatment and maintenance strategies for Asian patients.

DISCLOSURES

The authors disclosed receipt of an unrestricted educational grant from CeraVe International for support with this work's research. The authors also received consultancy fees for their work on this project.

All authors contributed to the development and review of this work and agreed with the content.

REFERENCES

1. Rocha M, Sanudo A, Bagatin E. The effect on acne quality of life of topical azelaic acid 15% gel versus a combined oral contraceptive in adult female acne: A randomized trial. *Dermatoendocrinol.* 2017;9(1):e1361572.
2. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol.* 2013;168(3):474-85.
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163-96.
4. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol.* 2015;172 Suppl 1:3-12.
5. Rocha MA, Bagatin E. Adult-onset acne: prevalence, impact, and management challenges. *Clin Cosmet Investig Dermatol.* 2018;11:59-69.
6. Hay RJ, Johns NE, Williams HC, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol.* 2014;134(6):1527-34.
7. Gieler U, Gieler T, Kupfer JP. Acne and quality of life - impact and management. *J Eur Acad Dermatol Venereol.* 2015;29 Suppl 4:12-4.
8. Walker N, Lewis-Jones MS. Quality of life and acne in Scottish adolescent schoolchildren: use of the Children's Dermatology Life Quality Index (CDLQI) and the Cardiff Acne Disability Index (CADI). *J Eur Acad Dermatol Venereol.* 2006;20(1):45-50.
9. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(1 Suppl):S1-37.
10. Dreno B, Thiboutot D, Gollnick H, et al. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol.* 2010;49(4):448-56.
11. Pawin H, Beylot C, Chivot M, et al. Creation of a tool to assess adherence to treatments for acne. *Dermatology.* 2009;218(1):26-32.
12. Francis NA, Entwistle K, Santer M, Layton AM, Eady EA, Butler CC. The management of acne vulgaris in primary care: a cohort study of consulting and prescribing patterns using the Clinical Practice Research Datalink. *Br J Dermatol.* 2017;176(1):107-15.
13. Angelova-Fischer I, Rippke F, Fischer TW, Neufang G, Zillikens D. A double-blind, randomized, vehicle-controlled efficacy assessment study of a skin care formulation for improvement of mild to moderately severe acne. *J Eur Acad Dermatol Venereol.* 2013;27 Suppl 2:6-11.
14. Enshaieh S, Jooya A, Siadat AH, Iraji F. The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. *Indian J Dermatol Venereol Leprol.* 2007;73(1):22-5.
15. Abad-Casintahan F, Chow SK, Goh CL, et al. Toward evidence-based practice in acne: consensus of an Asian Working Group. *J Dermatol.* 2011;38(11):1041-8.
16. Sturm-O'Brien AK, Brissett AE, Brissett AE. Ethnic trends in facial plastic surgery. *Facial Plast Surg.* 2010;26(2):69-74.
17. Ho SG, Chan HH. The Asian dermatologic patient: review of common pigmentary disorders and cutaneous diseases. *Am J Clin Dermatol.* 2009;10(3):153-68.
18. Suh DH, Shin JW, Min SU, et al. Treatment-seeking behaviors and related epidemiological features in Korean acne patients. *J Korean Med Sci.* 2008;23(6):969-74.
19. Aramaki J, Kawana S, Effendy I, Happle R, Loffler H. Differences of skin irritation between Japanese and European women. *Br J Dermatol.* 2002;146(6):1052-6.
20. Choi JM, Lew VK, Kimball AB. A single-blinded, randomized, controlled clinical trial evaluating the effect of face washing on acne vulgaris. *Pediatr Dermatol.* 2006;23(5):421-7.
21. Choi YS, Suh HS, Yoon MY, et al. A study of the efficacy of cleansers for acne vulgaris. *J Dermatolog Treat.* 2010;21(3):201-5.
22. Dreno B, Bensadoun RJ, Humbert P, et al. Algorithm for dermocosmetic use in the management of cutaneous side-effects associated with targeted therapy in oncology. *J Eur Acad Dermatol Venereol.* 2013;27(9):1071-80.
23. Goh CL, Noppakun N, Micali G, et al. Meeting the Challenges of Acne Treatment in Asian Patients: A Review of the Role of Dermocosmetics as Adjunctive Therapy. *J Cutan Aesthet Surg.* 2016;9(2):85-92.
24. Draelos ZD. The art and science of new advances in cosmeceuticals. *Clin Plast Surg.* 2011;38(3):397-407, vi.
25. Peirano RI, Hamann T, Dusing HJ, et al. Topically applied L-carnitine effectively reduces sebum secretion in human skin. *J Cosmet Dermatol.* 2012;11(1):30-6.
26. Chularojanamontri L, Tuchinda P, Kulthanan K, Varothai S, Winayanuwattikun W. A double-blinded, randomized, vehicle-controlled study to access skin tolerability and efficacy of an anti-inflammatory moisturizer in treatment of acne with 0.1% adapalene gel. *J Dermatolog Treat.* 2016;27(2):140-5.
27. Thiboutot D, Del Rosso JQ. Acne Vulgaris and the Epidermal Barrier: Is Acne Vulgaris Associated with Inherent Epidermal Abnormalities that Cause Impairment of Barrier Functions? Do Any Topical Acne Therapies Alter the Structural and/or Functional Integrity of the Epidermal Barrier? *J Clin Aesthet Dermatol.* 2013;6(2):18-24.
28. Lynde C, Tan J, Andriessen A, et al. Clinical Insights About the Role of pH in acne. *J Drugs Dermatol.* 2019;18(12):221.
29. Lain E, Andriessen AE. Choosing the Right Partner: Complementing Prescription Acne Medication With Over-the-Counter Cleansers and Moisturizers. *J Drugs Dermatol.* 2020;19(11):1069-75.
30. Cheng CE, Irwin B, Mauriello D, Liang L, Pappert A, Kimball AB. Self-reported acne severity, treatment, and belief patterns across multiple racial and ethnic groups in adolescent students. *Pediatr Dermatol.* 2010;27(5):446-52.
31. Pawin H, Chivot M, Beylot C, et al. Living with acne. A study of adolescents' personal experiences. *Dermatology.* 2007;215(4):308-14.
32. Feldman SR, Chen DM. How patients experience and manage dryness and irritation from acne treatment. *J Drugs Dermatol.* 2011;10(6):605-8.
33. Munehiro A, Murakami Y, Shirahige Y, et al. Combination effects of cosmetic moisturisers in the topical treatment of acne vulgaris. *J Dermatolog Treat.* 2012;23(3):172-6.
34. Hayashi N, Kawashima M. Study of the usefulness of moisturizers *on adherence of acne patients treated with adapalene.* J Dermatol. 2014;41(7):592-7.
35. Matsunaga K, Leow YH, Chan R, Kerrouche N, Paliargues F. Adjunctive usage of a non-comedogenic moisturizer with adapalene gel 0.1% improves local tolerance: a randomized, investigator-blinded, split-face study in healthy Asian subjects. *J Dermatolog Treat.* 2013;24(4):278-82.
36. Chularojanamontri L, Tuchinda P, Kulthanan K, Pongparit K. Moisturizers for Acne: What are their Constituents? *J Clin Aesthet Dermatol.* 2014;7(5):36-44.
37. Bikowski J. The use of therapeutic moisturizers in various dermatologic disorders. *Cutis.* 2001;68(5 Suppl):3-11.
38. Angelova-Fischer I, Rippke F, Peirano RI, Hamann T, Dusing HJ, et al. Topically applied L-carnitine effectively reduces sebum secretion in human skin. *J Cosmet Dermatol.* 2012;11:30–6.
39. Andriessen A, Rodas Diaz AC, Gameros PC, Macias O, Neves JR, Gonzalez CG. Over the Counter Products for Acne Treatment and Maintenance in Latin America: A Review of Current Clinical Practice. *J Drugs Dermatol.* 2021;20(3):244-50.

AUTHOR CORRESPONDENCE

Anneke Andriessen

E-mail:..... anneke.a@tiscali.nl

doi:10.36849/JDD.6329

November 2021 1222 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Patient-Reported Disease Burden and Unmet Therapeutic Needs in Atopic Dermatitis

Elizabeth D. Bacci PhD,[a] Anne M. Rentz MSPH,[b] Julia Correll MPH,[a] Evangeline J. Pierce PhD,[c] Amy M. DeLozier MPH,[c] Maria Jose Rueda MD,[d] Wendy Smith Begolka MBS,[e] Lisa Butler MBA[e]

[a]Patient-Centered Research, Evidera, Seattle, WA
[b]Patient-Centered Research, Evidera, Bethesda, MD
[c]Global Patient Outcomes and Real World Evidence, Eli Lilly and Company, Indianapolis, IN
[d]Medical Affairs, Eli Lilly and Company, Indianapolis, IN
[e]National Eczema Association, Novato, CA

ABSTRACT

Background: Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease causing a variety of dermatologic signs and symptoms, affecting patient's quality of life. While treatment options are available, they are of variable effectiveness. This study sought to characterize patient-reported AD signs and symptoms, flare, and associated bother, by disease severity and control.

Methods: Adults diagnosed with AD were recruited through the National Eczema Association (NEA) and clinical sites and completed a web-based survey including the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD), Recap of Atopic Eczema (RECAP), and Skin Pain numeric rating scale (NRS), as well as questions on previous/current clinical presentation, flare frequency and severity, past/present AD treatment, and sociodemographic characteristics.

Results: A total of 186 participants completed the survey (mean age 39.7 years, 80% female). The most frequently reported current AD signs and symptoms included dryness, itch, redness, roughness, and flaking skin, and the most bothersome were itch, dryness, and redness (63%). The majority of participants (84%) were either currently experiencing a flare or had experienced one within the past month. The most common signs and symptoms that grew worse during the most recent flare were itch and redness across all disease severity groups. Participants most often experienced one to three flares in the last three months. Flare frequency, duration, and average severity increased with greater disease severity and lack of disease control.

Conclusions: The results of this study demonstrate the diverse and considerable symptomatic burden experienced by people with AD, even while being treated for AD.

J Drugs Dermatol. 2021;20(11):1222-1230. doi:10.36849/JDD.6329

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease, with a prevalence in the United States (US) of 7.3%.[1] AD causes a variety of dermatologic signs and symptoms, resulting in numerous impacts on quality of life, such as sleep disturbance due to itching,[2] and can negatively impact patients' emotional and social functioning, and impede occupational and academic pursuits.[3]

Standard approaches to treatment typically include basic skin care and emollient agents, topical corticosteroid therapy and topical calcineurin inhibitors, which may be supplemented by the addition of phototherapy, off-label immunosuppressants, or the biologic, dupilumab.[4,5] Dupilumab is currently the only FDA-approved biologic for AD in the US; a number of new systemic treatments are anticipated to become available in the US later this year[6,7] A recent consensus guidance recommends systemic therapy be considered for patients with AD after considering both disease severity and impact of AD on quality of life.[8]

Given the evolving treatment landscape and prescribing guidance, it is important to understand the symptomatic experience from the patient's viewpoint, including perceived control of AD symptoms and the nature and frequency of AD flares. While flare triggers and flare management are an important aspect of AD, limited research has been conducted on flare severity and symptomology, especially in those currently treated for AD. Moreover, there is lack of consistency in how flares are defined in AD studies.[9]

The primary objective of this study was to gain a greater understanding of AD signs and symptoms, flares, and associated bother to patients with AD. Of further interest was to characterize the association of the symptomatic experience by disease severity and control.

MATERIALS AND METHODS

Study Design and Procedures

This study was a cross-sectional, non-interventional, web-based survey with adult participants with AD living in the US. To be eligible, individuals must have been diagnosed with AD at least one year before screening. Individuals were excluded if they had a current or historic diagnosis of lupus erythematosus, psoriasis, or skin cancer. The study received institutional review board (IRB) approval from Advarra IRB (Columbia, Maryland; Advarra study number: Pro00041638).

A two-pronged recruitment approach was taken, including recruitment through the National Eczema Association (NEA) and clinical sites. Participants from NEA were recruited through IRB-approved advertisements in NEA e-newsletters during September 2020. Screening questions were used to determine their eligibility. Participants were also recruited from four clinical sites in the US. Clinical site staff identified potential participants by reviewing patient charts/databases or speaking to patients during clinical visits. Clinical site staff completed eligibility and confirmation of clinical diagnosis forms for these participants.

During screening, all participants were asked about AD systemic therapy use in the past two years; a recruitment target was established so no more than 25% of the sample would have not been offered or recommended systemic therapy for AD. Eligible participants were provided a link to the web survey. Participants who completed the survey were remunerated.

Participants provided electronic consent to participate prior to beginning the survey. The survey was provided in US English and consisted of the Patient Oriented Eczema Measure (POEM),[10] Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD),[11] Recap of Atopic Eczema (RECAP), a Skin Pain numeric rating scale (NRS), sociodemographic characteristics, clinical presentation, and AD treatment questions. A granular assessment of the AD symptomatic experience, including current/past experience of a range of symptoms, and associated symptom severity and bother also was conducted. Participants reported on flares (including severity and frequency), defined as "your symptoms become worse, new symptoms develop, or a symptom is experienced at a new location. Common signs and symptoms include itching, skin pain, redness, and dryness."

Statistical Analyses

All statistical analyses were performed using SAS/STAT®, version 9.1.3 (SAS Institute Inc., Cary, NC USA). Descriptive analyses were used to characterize the distribution properties of each variable overall and by disease severity (defined by the PO-SCORAD). PO-SCORAD total scores of ≤27 indicate mild AD; ≥28-≤56 indicate moderate AD; and ≥57 indicate severe AD.[12] Differences in flares were assessed by disease severity and control (as measured by the RECAP). The study authors established RECAP control ranges based on the POEM bandings:[13] scores of 0-7 indicate moderately controlled to controlled disease; 8-16 indicate mildly uncontrolled disease; and 17–28 indicate uncontrolled disease.

For continuous variables, mean, median, standard deviation (SD), and range were calculated; frequency and percent distribution by category were calculated for categorical variables. General linear models were used to evaluate differences across continuous variables; chi-square tests were used to evaluate differences across groups for categorical data. All statistical tests used a two-sided significance level of 0.05.

RESULTS

Sample Disposition and Demographic Characteristics

A total of 389 participants entered the survey, of which 183 were ineligible. Reasons for exclusion did not significantly differ by recruitment mode. Twenty participants who were eligible did not complete the survey. A total of 186 participants completed the survey, including 111 recruited by NEA and 75 recruited through clinical sites; all were included in the final survey sample. Of these, 72% (n=80) of those recruited through NEA and 63% (n=47) of those recruited from clinical sites had been offered or recommended a systemic medication for AD.

The demographic characteristics of survey respondents, stratified by disease severity, are found in Table 1. Of 186 participants (38 men/148 women) the majority were White (53%), followed by Asian (29%), and Black or African American (12%). Fifty participants (27%) were classified as having mild AD, 83 (45%) moderate AD, and 49 (26%) severe AD (four participants are missing severity categorization due to at least one missing PO-SCORAD item). Participants first noticed signs/symptoms of AD most often between one and 12 years old (45%) and less than one year old (17%), which was similar by severity group. Almost 25% of participants, regardless of severity, first noticed signs and symptoms at age 21 or older.

Symptomatic Experience and Disease Control

Symptom Experience and Severity

The mean PO-SCORAD total score was 42.1 (SD=20.5; range=3.5-90.2). Mean scores for the RECAP, Skin Pain NRS, and trouble sleeping VAS were found to be significantly higher in those with greater disease severity (P<0.0001; Figure 1). The most common current symptoms for participants across all AD severities were dryness (62% mild AD, 96% moderate AD, 98% severe AD; Figure 2) and itch (46%, 90%, and 98%, respectively). Participants with severe AD were more likely to be currently experiencing every symptom queried.

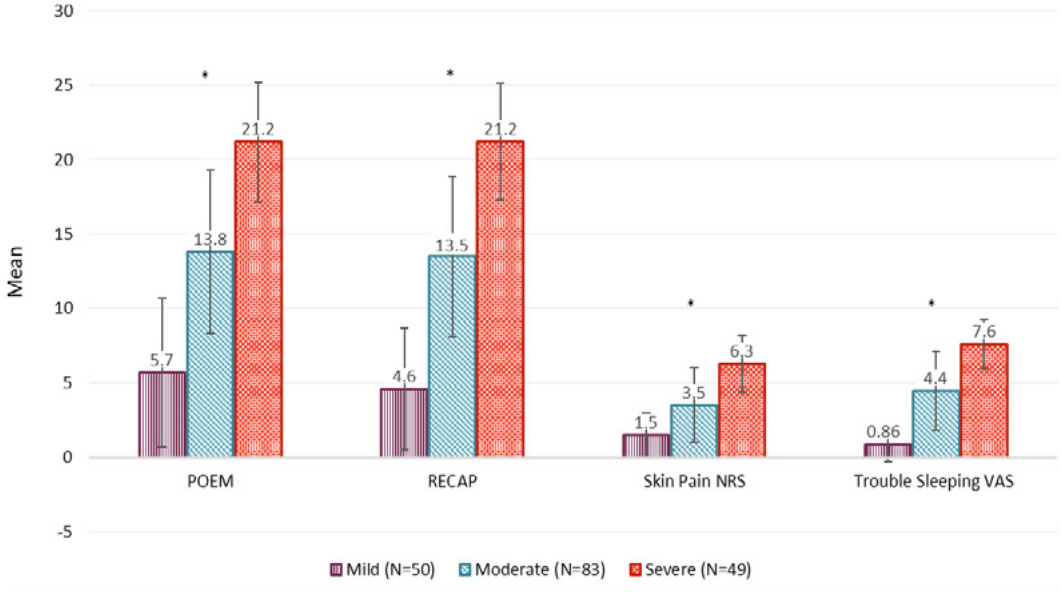
Reported bother of previous/current AD signs and symptoms by severity group are found in Figures 3a-3c; bother increased by severity group. The most bothersome were itch (reported

TABLE 1.

Demographic Characteristics					
	Total (N=186)[a]	Mild[b] (N=50)	Moderate[b] (N=83)	Severe[b] (N=49)	*p*-value
Median Age (range)	37.0 (18.0–72.0)	44.0 (18.0–72.0)	38.0 (18.0–71.0)	31.0 (18.0–72.0)	--
Mean (SD)	39.7 (15.3)	42.8 (16.5)	40.6 (14.9)	35.1 (13.5)	0.0311
Male, n (%)	38 (20.4%)	12 (24.0%)	13 (15.7%)	11 (22.4%)	0.4343
Race, n (%)	--	--	--	--	--
White	99 (53.2%)	35 (70.0%)	47 (56.6%)	16 (32.7%)	0.0008
Black or African American	23 (12.4%)	8 (16.0%)	8 (9.6%)	7 (14.3%)	0.5198
Asian	54 (29.0%)	5 (10.0%)	25 (30.1%)	22 (44.9%)	0.0006
Other[c]	20 (10.8%)	5 (10.0%)	9 (10.8%)	5 (10.2%)	0.9862
Hispanic or Latino, n (%)	18 (9.7%)	6 (12.0%)	6 (7.2%)	6 (12.2%)	0.5449
Education, n (%)	--	--	--	--	--
High school graduate	11 (5.9%)	2 (4.0%)	4 (4.8%)	5 (10.2%)	0.3534
Some college or college degree	175 (94.1%)	48 (96.0%)	79 (95.2%)	44 (89.8%)	--
Age when individual noticed symptoms, or parent observed signs, of atopic dermatitis/eczema? n (%)					
<1 year	31 (16.7%)	5 (10.0%)	20 (24.1%)	5 (10.2%)	0.0876
1–12 years	84 (45.1%)	22 (44.0%)	31 (37.4%)	30 (61.2%)	
13–20 years	26 (14.0%)	7 (14.0%)	11 (13.3%)	7 (14.3%)	
21–40 years	22 (11.8%)	8 (16.0%)	9 (10.8%)	5 (10.2%)	
≥41 years	23 (12.4%)	8 (16.0%)	12 (14.5%)	2 (4.1%)	

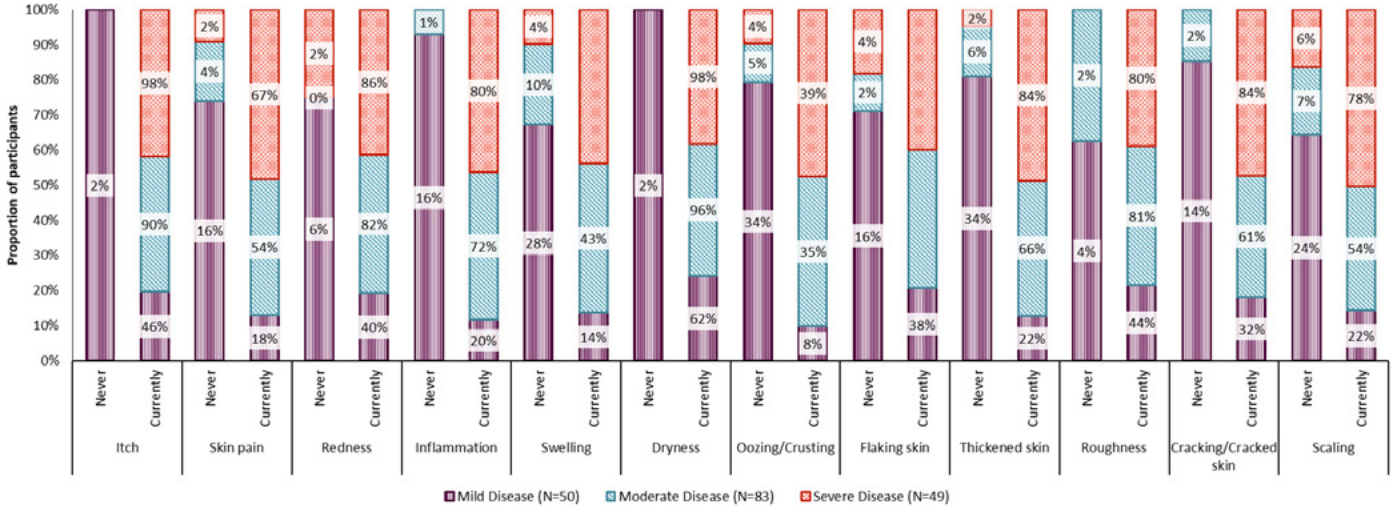
SD=standard deviation
[a]Four participants are missing severity level categorization due to at least one missing item on the PO-SCORAD.
[b]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD.
[c]Other race: Mixed Race (n=8), Hispanic (n=4), American Indian or Alaska Native (n=3), Native Hawaiian or Other Pacific Islander (n=3), Middle Eastern (n=2), Filipino (n=1), and 'not applicable' (n=2).

FIGURE 1. Disease Burden by AD Severity[a]



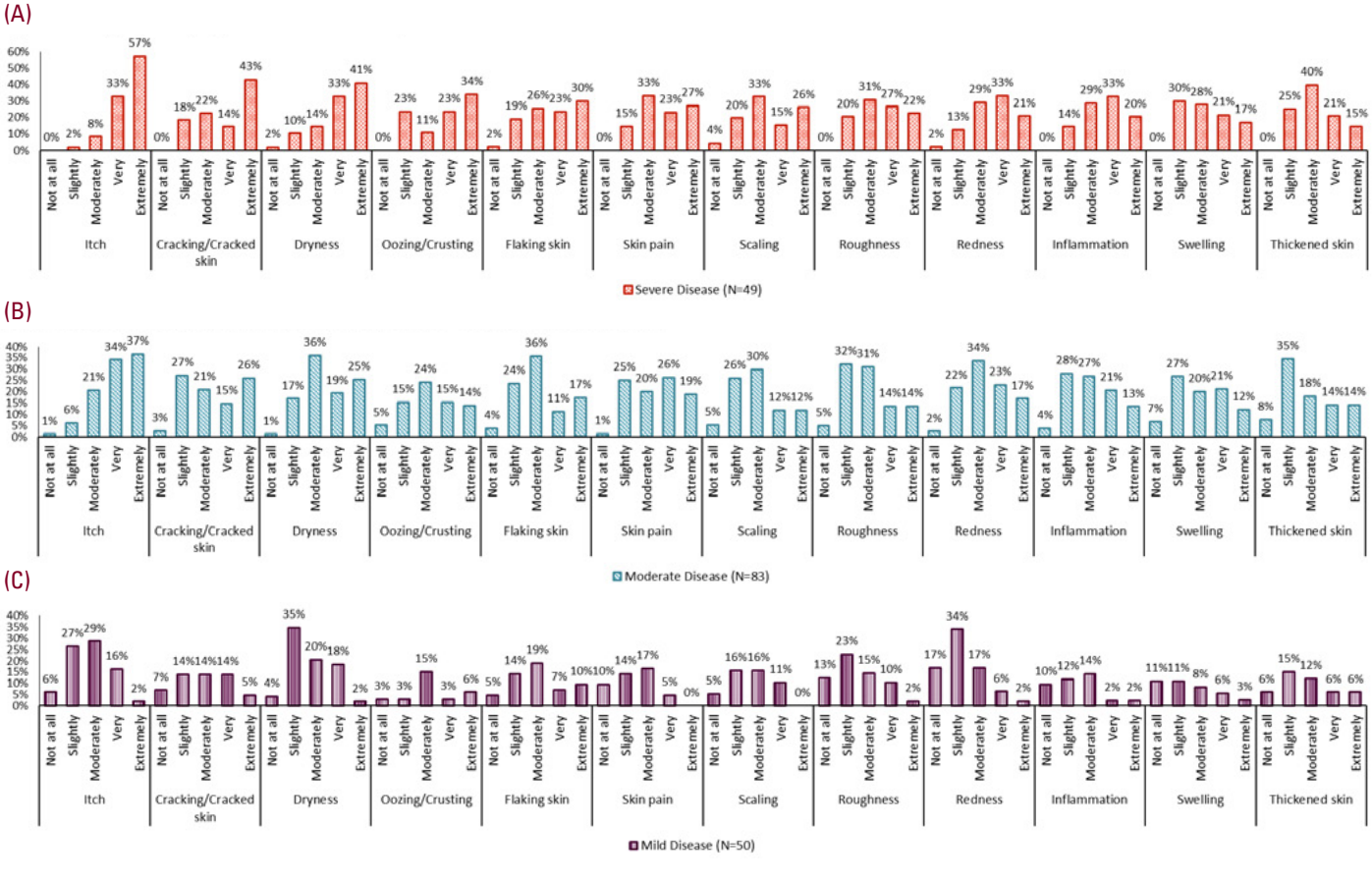
*Overall comparison is significant at <0.0001.
[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD. Four participants are missing severity level categorization due to at least one missing item on the PO-SCORAD.

FIGURE 2. AD Signs and Symptoms by AD Severity[a]



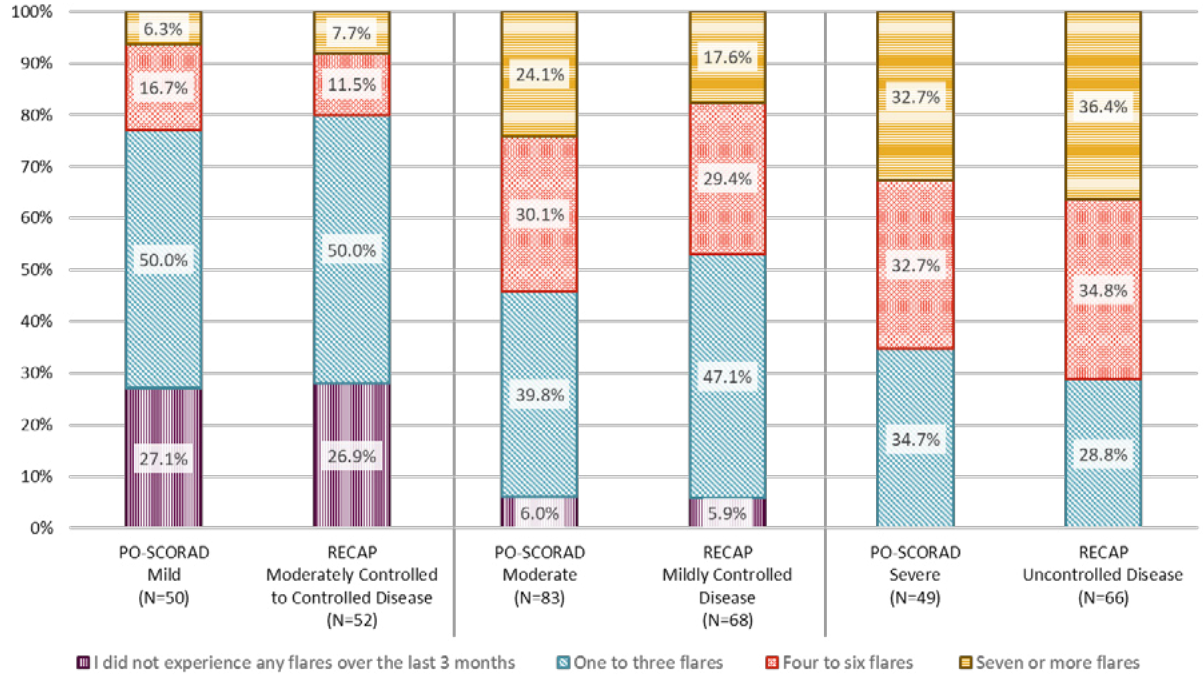
[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD. Four participants are missing severity level categorization due to at least one missing item on the PO-SCORAD.

FIGURE 3. (A) Symptoms/Sign Bother for Participants with Severe Disease. (B) Symptoms/Sign Bother for Participants with Moderate Disease. (C) Symptoms/Sign Bother for Participants with Mild Disease.



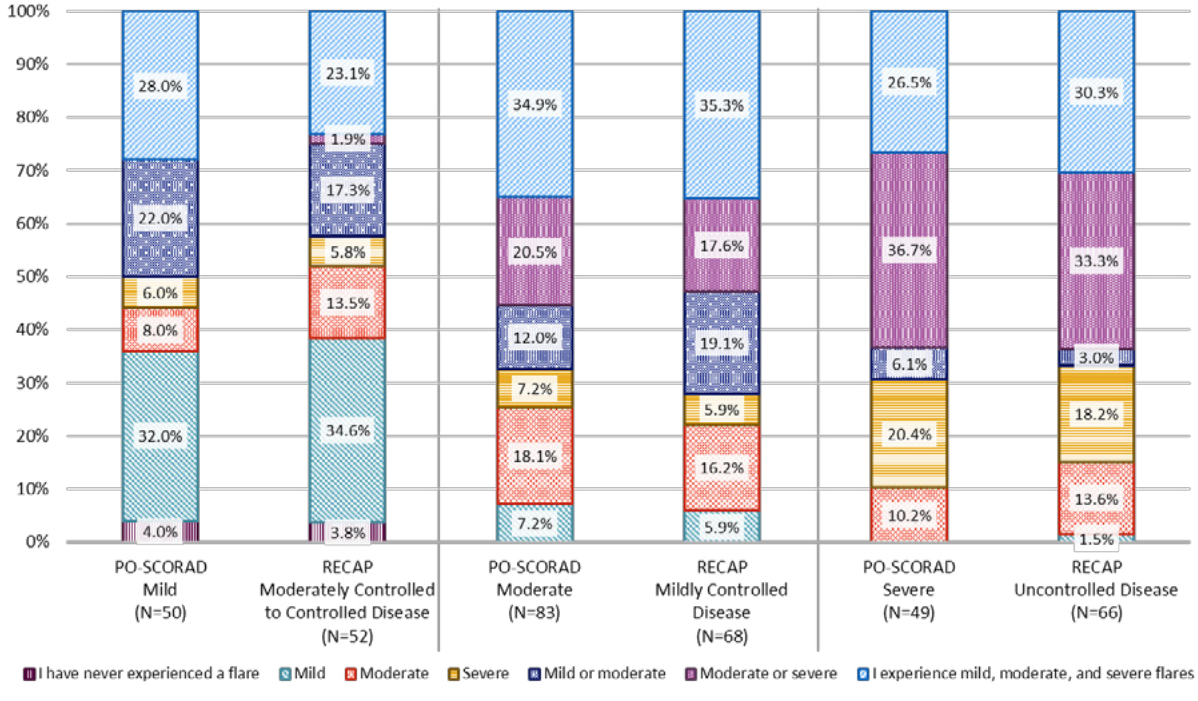
[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD. Four participants are missing severity level categorization due to at least one missing item on the PO-SCORAD.

FIGURE 4A. 3–Month Flare Frequency by Disease Severity (PO-SCORAD) and Disease Control (RECAP)[a]



[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD. Disease control determined by RECAP scores: ≤7 indicate moderately controlled to controlled disease; 8–16 indicate mildly controlled disease; ≥17 indicate uncontrolled disease.

FIGURE 4B. Flare Severity by Disease Severity (PO-SCORAD) and Disease Control (RECAP)[a]



[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD. Disease control determined by RECAP scores: ≤7 indicate moderately controlled to controlled disease; 8–16 indicate mildly controlled disease; ≥17 indicate uncontrolled disease.

TABLE 2.

Characteristics of AD Flares by AD Severity[a,b] and Control

	PO-SCORAD Categories[a]				RECAP Categories			
	Mild (N=50)	Moderate (N=83)	Severe (N=49)	*p*-value	Moderately controlled to controlled disease (N=52)	Mildly controlled disease (N=68)	Uncontrolled disease (N=66)	*p*-value
Duration of flares (any severity) over last 3 months, n (%)								
Did not experience any flares	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.0001	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0004
Typically < 1 per day	7 (20.0%)	1 (1.3%)	0 (0.0%)		5 (13.9%)	3 (4.7%)	0 (0.0%)	
- 1–3 days	13 (37.1%)	25 (32.1%)	7 (14.3%)		15 (41.7%)	24 (37.5%)	8 (12.1%)	
- 4-7 days	4 (11.4%)	19 (24.4%)	13 (26.5%)		6 (16.7%)	11 (17.2%)	19 (28.8%)	
- 1–2 weeks	4 (11.4%)	12 (15.4%)	13 (26.5%)		5 (13.9%)	9 (14.1%)	15 (22.7%)	
- >2 weeks	7 (20.0%)	21 (26.9%)	16 (32.7%)		5 (13.9%)	17 (26.6%)	24 (36.4%)	
When was your last flare (during last three months)? n (%)								
Experiencing a flare now	12 (34.3%)	34 (43.6%)	34 (69.4%)	0.0201	8 (22.2%)	28 (43.8%)	44 (66.7%)	<0.0001
One month ago or less	16 (45.7%)	31 (39.7%)	11 (22.4%)		17 (47.2%)	29 (45.3%)	14 (21.2%)	
Two months ago	3 (8.6%)	8 (10.3%)	4 (8.2%)		5 (13.9%)	6 (9.4%)	6 (9.1%)	
Three months ago	4 (11.4%)	5 (6.4%)	0 (0.0%)		6 (16.7%)	1 (1.6%)	2 (3.0%)	
How severe is your current flare (or most recent flare if you are not currently experiencing a flare)? n (%)								
Mild	23 (65.7%)	20 (25.6%)	3 (6.1%)	<0.0001	25 (69.4%)	20 (31.3%)	2 (3.0%)	<0.0001
Moderate	11 (31.4%)	41 (52.6%)	28 (57.1%)		11 (30.6%)	36 (56.3%)	36 (54.5%)	
Severe	1 (2.9%)	17 (21.8%)	18 (36.7%)		0 (0.0%)	8 (12.5%)	28 (42.4%)	
For most recent flare, which signs/symptoms grew worse?[c] n (%)								
Itch	25 (71.4%)	73 (93.6%)	47 (95.9%)	0.0010	27 (75.0%)	59 (92.2%)	62 (93.9%)	0.0130
Skin pain	10 (28.6%)	44 (56.4%)	26 (53.1%)	0.0251	7 (19.4%)	36 (56.3%)	37 (56.1%)	0.0009
Redness	15 (42.9%)	52 (66.7%)	32 (65.3%)	0.0215	15 (41.7%)	43 (67.2%)	42 (63.6%)	0.1061
Inflammation	11 (31.4%)	47 (60.3%)	26 (53.1%)	<0.0001	12 (33.3%)	36 (56.3%)	36 (54.5%)	0.0001
Swelling	6 (17.1%)	19 (24.4%)	13 (26.5%)	0.0323	7 (19.4%)	15 (23.4%)	16 (24.2%)	0.0797
Dryness	13 (37.1%)	48 (61.5%)	28 (57.1%)	0.0512	15 (41.7%)	35 (54.7%)	41 (62.1%)	0.1398
Oozing/Crusting	4 (11.4%)	22 (28.2%)	20 (40.8%)	<0.0001	5 (13.9%)	17 (26.6%)	24 (36.4%)	0.0004
Flaking skin	9 (25.7%)	40 (51.3%)	29 (59.2%)	0.0034	13 (36.1%)	30 (46.9%)	37 (56.1%)	0.1005
Thickened skin	5 (14.3%)	16 (20.5%)	20 (40.8%)	<0.0001	4 (11.1%)	14 (21.9%)	23 (34.8%)	0.0043

SD=standard deviation
[a]Severity determined by PO-SCORAD scores: ≤27 indicate mild AD; ≥28 to ≤56 indicate moderate AD; ≥57 indicates severe AD.
[b]Four participants are missing severity level categorization due to at least one missing item on the PO-SCORAD.
[c]Responses not mutually exclusive.

as moderately, very, or extremely bothersome by 81% of all participants), dryness (71%), and redness (63%). These were also the most bothersome symptoms for participants with severe (Figure 3a) and moderate (Figure 3b) AD, though participants with severe AD also reported skin pain and inflammation to be among the most bothersome. Participants with mild AD reported itch, dryness, and flaking skin as their most bothersome symptoms (Figure 3c).

The participants who reported currently experiencing a symptom were asked to rate its severity when at its worst (data not shown). Itch was most often reported as severe at its worst. Seventy-one percent of all participants currently experiencing itch rated it as severe when at its worst, but the proportion varied by severity group: 90% of participants with severe AD, 72% with moderate AD, and 35% with mild AD rated their current itch as severe. Dryness was rated as severe at its worst by 59%

of all participants (77% of participants with severe AD, 59% with moderate AD, and 36% with mild AD).

The frequency, severity, and bother of AD symptoms were also examined by severity group for participants on topical (n=169) and systemic medications (n=111) (data not shown). Since 105 (57%) participants were currently using both topical and systemic medication, there is considerable overlap between the groups. However, AD symptom presentation was similar by treatment type (data not shown).

AD Flares

Flare frequency increased with AD severity, though participants in all severity groups most often experienced 1–3 flares in the last three months (35% of participants with severe AD, 40% of moderate, and 48% of mild) (Figure 4a). Participants with less controlled AD reported significantly (P<0.0001) more frequent flares (Figure 4a). The pattern of flare frequency by disease control paralleled the pattern by disease severity: mild disease severity responses were highly similar to those with moderately controlled to controlled disease, responses for moderate disease paralleled those considered mildly controlled, and severe responses were similar to those with uncontrolled disease.

Overall, average flare severity increased with AD severity (P<0.0001; Figure 4b). Participants with severe AD most often reported experiencing moderate or severe flares (37%), while 27% reported some mild, moderate, and severe flares. Participants with moderate AD were most likely to report flares of mixed severity (35%) or moderate/severe (21%); participants with mild AD were most likely to report mild flares (32%) or mixed severity (28%). A similar pattern was found when flare severity was stratified by AD control (Figure 4b).

Participants with moderately controlled to controlled disease and mildly controlled disease most often reported their most recent flares lasting 1–3 days (42% and 38%, respectively), while participants with uncontrolled disease most often reported flares lasting longer than two weeks (36%) (Table 2). The majority of participants (84%) were either currently experiencing a flare or had experienced one within the past month. Flare severity was reported as mild by participants with moderately controlled to controlled disease (69%), and moderate by participants with mildly controlled disease (56%) or uncontrolled disease (55%). Results by AD severity paralleled those by control status for these flare characteristics.

Itch and redness were the most commonly reported symptoms that grew worse during recent flares across all severity groups (Table 2). Participants with mild and moderate AD reported dryness as the third most common symptom (37% and 62%, respectively); participants with severe AD reported flaking skin as theirs (59%). Results by AD control status paralleled results by disease severity status.

DISCUSSION

This study is one of few to quantify the burden of signs, symptoms and flares experienced by a diverse sample of patients with AD. A number of studies have reported on the health-related quality of life burden of AD, but fewer examine it along with other indicators of morbidity such as patient-reported symptoms, symptom severity, disease severity, and disease control.[1,14,15] A newly validated PO-SCORAD severity strata[16] was used to stratify the current sample by severity level. The result was a mix of AD severity levels with a similar proportion of moderate patients (45%) and a higher proportion of severe patients (26%) than a previous AD burden study.[14] Eckert and colleagues used the US National Health and Wellness Survey data and reported on a sample of 40% moderate and only 11% severe people with AD.[14] The higher proportion of severe patients in the current study most likely was due to a recruitment limit on participants with recent use of systemic medication. Recruiting in this manner allowed for a better understanding of frequency and bother of symptoms that may only be experienced by more severe patients who were offered or recommended systemic medication.

Participants with AD across all severity levels report a high symptomatic burden, with more than 85% experiencing the twelve symptoms characteristic of the disease that were assessed in this study. Similar to other studies,[1,8,17,18] patients reported itch as a frequent and bothersome problem. Although itch was the most frequent and bothersome symptom in previous studies,[1,18] dryness was the most frequently reported symptom patients experienced in this study. The symptoms reported are often severe and bothersome to participants; of those who experienced the symptom during the last three months, all symptoms were reported as at least moderately bothersome by 48%. This high symptom burden was reported despite 97% reporting treatment with either a topical or systemic medication, suggesting current medication is not adequately treating the symptoms.

While there is a need in the literature for a more standard definition of flare,[19,20] there is some agreement that any definition should delineate between disease activity and disease severity, and should include some type of patient-reported outcomes and "behavioral measure, such as escalation of treatment."[20] AD clinical trials define flare-related endpoints in various ways, including an arbitrary cutoff on an existing severity scale, composite definition,[19] and an escalation of treatment.[21] Flares were self-reported in the current study, defined as either symptoms worsening, new symptoms developing, or a symptom experienced in a new location. Across severity and control groups, over two-thirds of participants reported at least one flare in the past three months, and flares increased in frequency as severity increased or control decreased. These

study results align with others which found flare frequency and duration increases with AD severity,[22,23] adding information on specific signs and symptoms that worsen during flares, flare severity, and by examining flare characteristics by disease control.

There are several limitations to the study design and results. Although care was taken to conduct the survey in a scientifically rigorous manner, anonymous web-based data collection processes prevent clinician verification of diagnoses and other clinical data. To overcome this limitation, participants were recruited through two avenues, one of which was clinical sites. This additional recruitment method allowed a confirmation of clinician diagnosis in 40% of the sample. Despite the two recruitment avenues, participants were similar in most sociodemographic and clinical characteristics. However, all symptoms were self-reported by participants and are subject to self-report and recall bias.[24] Additionally, the generalizability of the results may be limited due to convenience sampling. Last, this research should be replicated in other geographic locations outside of the US, where patients will experience different health care systems and diagnoses and treatment patterns.

CONCLUSION

This study demonstrates the diverse and considerable symptomatic burden experienced by people with AD, even while receiving treatment. Increased awareness of symptomatic burden, flare frequency and duration, and unmet treatment needs is important for healthcare providers when treating AD patients of any severity level.

DISCLOSURES

The study sponsor was involved in the design of the analysis, interpretation of the data, and review and approval of the manuscript. No other conflicts of interest were reported.

Elizabeth Bacci, Anne Rentz, and Julia Correll are employed by Evidera, which provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. In their salaried positions, they work with a variety of companies and organizations and are precluded from receiving any payment or honoraria directly from these organizations for services rendered.

Evangeline Pierce, Amy DeLozier, and Maria Jose Rueda are employed by and own stock in Eli Lilly and Company.

Wendy Smith Begolka and Lisa Butler are employed by the National Eczema Association, which does receive sponsorship funding (not related to this project) from Eli Lilly.

Funding: Eli Lilly and Company provided the funding for the study and for the manuscript.

ACKNOWLEDGMENT

This work was supported by funding from Eli Lilly and Company, Indianapolis, IN. The authors would like to thank Andrea Schulz for her assistance in executing the study, Yulia Savva and Jun Chen for analysis assistance, and Fritz Hamme for editorial and production assistance. We also would like to thank Kawthar Nakayima for her amazing ability to create graphs and figures. Authors gratefully acknowledge the support of the people suffering with AD who participated in this study.

REFERENCES

1. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol.* 2018a;121(3):340-347.
2. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. *J Eur Acad Dermatol Venereol.* 2014;28(6):719-726.
3. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.
4. American Academy of Dermatology Association (AAD). Atopic dermatitis clinical guideline. American Academy of Dermatology Association (AAD),. https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis. Published 2021. Accessed 1 June, 2021.
5. Seegraber M, Srour J, Walter A, Knop M, Wollenberg A. Dupilumab for treatment of atopic dermatitis. *Expert Rev Clin Pharmacol.* 2018;11(5):467-474.
6. Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib. *Drugs Context.* 2020;9.
7. Newsom M, Bashyam AM, Balogh EA, Feldman SR, Strowd LC. New and emerging systemic treatments for atopic dermatitis. *Drugs.* 2020;80(11):1041-1052.
8. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol.* 2017;77(4):623-633.
9. Langan SM, Thomas KS, Williams HC. What is meant by a "flare" in atopic dermatitis? A systematic review and proposal. *Arch Dermatol.* 2006;142(9):1190-1196.
10. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol.* 2004;140(12):1513-1519.
11. Vourc'h-Jourdain M, Barbarot S, Taieb A, et al. Patient-oriented SCORAD: a self-assessment score in atopic dermatitis. A preliminary feasibility study. *Dermatology.* 2009;218(3):246-251.
12. Stalder JF, Barbarot S, Wollenberg A, et al. Patient-oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy.* 2011;66(8):1114-1121.
13. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol.* 2013;169(6):1326-1332.
14. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. *J Am Acad Dermatol.* 2017;77(2):274-279 e273.
15. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic dermatitis in america study: a cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. *J Invest Dermatol.* 2019;139(3):583-590.
16. Silverberg JI, Gelfand JM, Margolis DJ, et al. Severity strata for POEM, PO-SCORAD, and DLQI in US adults with atopic dermatitis. *Ann Allergy Asthma Immunol.* 2018b;121(4):464-468 e463.
17. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. *Br J Dermatol.* 2009;160(3):642-644.
18. Wittkowski A, Richards HL, Griffiths CE, Main CJ. Illness perception in individuals with atopic dermatitis. *Psychol Health Med.* 2007;12(4):433-444.

19. Langan SM, Schmitt J, Williams HC, Smith S, Thomas KS. How are eczema 'flares' defined? A systematic review and recommendation for future studies. *Br J Dermatol.* 2014;170(3):548-556.
20. Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. *Dermatol Clin.* 2017;35(3):291-297.
21. clinicaltrials.gov. Study to Assess the Efficacy and Long-term Safety of Dupilumab (REGN668/SAR231893) in Adult Participants With Moderate-to-Severe Atopic Dermatitis. US National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02260986. Published 2017. Updated 17 October 2017. Accessed 1 June, 2021.
22. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol.* 2006;118(1):226-232.
23. Wei W, Ghorayeb E, Andria M, et al. A real-world study evaluating adeQUacy of Existing Systemic Treatments for patients with moderate-to-severe Atopic Dermatitis (QUEST-AD): Baseline treatment patterns and unmet needs assessment. *Ann Allergy Asthma Immunol.* 2019;123(4):381-388 e382.
24. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc.* 2016;9:211-217.

AUTHOR CORRESPONDENCE

Elizabeth D. Bacci PhD
E-mail:..... Elizabeth.Bacci@evidera.com

doi:10.36849/JDD.6442

November 2021 1231 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Effectiveness and Safety of Calcium Hydroxylapatite With Lidocaine for Improving Jawline Contour

Amir Moradi MD,[a] Jeremy B. Green MD,[b] Joel L. Cohen MD,[c] John H. Joseph MD,[d] Rada Dakovic PhD,[e] Gemma Odena PhD,[f] Amit Verma PhD,[f] Richard Scher MD[f]

[a]Moradi MD, Vista, CA

[b]Skin Research Institute and Skin Associates of South Florida, Coral Gables, FL

[c]AboutSkin Dermatology and AboutSkin Research Greenwood Village and Lone Tree, CO; Department of Dermatology, University of California, Irvine, CA

[d]Clinical Testing Center of Beverly Hills, Encino, CA

[e]Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany

[f]Merz North America, Inc., Raleigh, NC

ABSTRACT

Background: One of the early signs of aging is loss of jawline contour. Not all cases require surgical intervention and soft-tissue augmentation with injectable fillers may restore the profile and youthful appearance of the jawline.

Objective: To demonstrate the effectiveness and safety of calcium hydroxylapatite with lidocaine [CaHA (+); Radiesse® (+)] to improve the contour of jawline after deep (subdermal and/or supraperiosteal) injection.

Methods: Healthy eligible patients with moderate or severe ratings on the Merz Jawline Assessment Scale (MJAS) were randomized 2:1 to treatment with CaHA (+) or to control. Patients in the control group remained untreated until week 12, then received delayed treatment. Touch-ups were allowed in both groups, and re-treatment was allowed in the treatment group only. Effectiveness was evaluated on the MJAS, patient and investigator Global Aesthetic Improvement Scales, and FACE-Q™ questionnaires. Adverse events were recorded over a 60-week period.

Results: Treatment response rate (≥1-point MJAS improvement) was 93/123 (75.6%) for the treatment group and 5/57 (8.8%) for the control/delayed-treatment group at week 12. The difference between response rates was statistically significant ($P<0.0001$), showing superiority of treatment over control. Satisfaction with aesthetic improvement was reported by patients and treating investigators throughout the study. A total of 76/113 (67.3%) patients who responded to treatment 12 weeks after initial injection also demonstrated persistent improvement 48 weeks after initial treatment. The study demonstrated a favorable safety profile, with no reported unexpected adverse events.

Conclusions: CaHA (+) is a safe and effective treatment for improving the contour of the jawline.

J Drugs Dermatol. 2021;20(11):1231-1238. doi:10.36849/JDD.6442

INTRODUCTION

Multiple factors, including hereditary and aging aspects, lead to a noticeable, undesirable contour of the jawline, such as loss of bone volume, fat atrophy (volume loss), and descent of fat.[1] Volume loss in relation to the attachment points of the skin to the underlying superficial muscular aponeurotic system and/or bone results in specific patterns of deflation, pseudoptosis, and shadowing – all of which characterize the aging face. As soft tissue fullness shifts from the upper face to the lower face, the aging face changes from a youthful heart-shaped appearance to a more rectangular shape.[2] A surgical facelift is the standard treatment used to address these signs of aging and aids in redefining the jawline. As the aesthetic market evolves, patients are increasingly seeking to enhance their appearance with less invasive procedures and reduced downtime.[3]

Soft tissue fillers may be injected to replenish volume and restore the contour of the jawline; fillers also provide an opportunity to enhance the prominence of the jaw by adding volume at the chin and/or on the sides of the jawline. This enhancement can be achieved through filling volume and contour deficits, repositioning of ptotic, superficial fat compartments, and tightening the skin around the jawline.[3,4] To reestablish or correct optimal jawline contour, a soft tissue filler with high elasticity and viscosity offers the best volumizing capacity.[2]

Over the last decade, multiple published reports have demonstrated that fillers, such as calcium hydroxylapatite (CaHA; Radiesse®, Merz North America, Raleigh, NC, USA) improve the appearance of the aging jawline.[4-11] The available

literature supports both the effectiveness and safety of CaHA for injection along the jawline, from the mentum to the mandibular angle. Multiple authors have reported favorable results 6- and 12-months after product placement, noting both investigator and patient satisfaction.[6-8,11-12] Few procedure-related adverse events, such as pain, erythema, edema, and bruising, were reported – most of which were mild and resolved quickly without intervention. Overall, the reported safety profile of CaHA for improving jawline contour is favorable and comparable to other established treatment indications.

The purpose of this large, robust, randomized pivotal study was to investigate the safety and effectiveness of CaHA with lidocaine [CaHA (+); Radiesse® (+), Merz North America, Raleigh, NC, USA] treatment in patients who desired improvement of moderate to severe loss of jawline contour and to support the recent US Food and Drug Administration (FDA) approval for this indication.

MATERIALS AND METHODS

Study Design

This was a 60-week, prospective, multicenter, randomized, controlled, rater-blinded, pivotal clinical study (ClinicalTrials.gov: NCT03583359).

All eligible patients were randomized (2:1 allocation ratio; Figure 1) to either treatment with CaHA (+) or to control/delayed treatment (ie, untreated controls until primary endpoint assessment at week 12, when the controls were eligible for treatment).

Patients randomized to the treatment group received an initial CaHA (+) injection in both the right and left jawline and were assessed at week 4 for a touch-up in one or both jawlines to achieve optimal correction. These patients returned at week 12 for their primary effectiveness assessment. Patients in the treatment group were eligible to receive re-treatment with CaHA (+) at week 48. Patients randomized to the control group remained untreated until completion of the primary endpoint assessment at week 12; subsequently, they were treated with CaHA (+) and assessed 4-weeks later for a touch-up. These patients were not offered re-treatment. All patients were followed for at least 48 weeks post initial treatment and until the end of the study to assess long-term effectiveness and safety.

Institutional review boards of all participating sites reviewed the protocol and approved the study before enrolling the first patient.

Patients

Patients were recruited at 15 sites within the United States. To be considered for study inclusion, male and female patients had to be between 22 and 65 years of age with right and left jawline ratings of 2 or 3 (moderate or severe) on the Merz Jawline Assessment Scale (MJAS) and have symmetrical jawlines.

Key exclusion criteria included non-age-related skin or fat atrophy in the midfacial and/or jawline region or diagnosis of a connective tissue disorder; skin laxity and/or sun damage beyond typical of the patient's age; prior surgery on the jaw or in the jawline area or a permanent implant or graft in the lower face and/or jawline area; previous treatment with fat injections, permanent fillers, or semi-permanent fillers in the lower face or jawline area; treatment with porcine-based collagen fillers or CaHA fillers in the lower face and/or jawline area received within 24 months prior to randomization; and administration

FIGURE 1. Study design. R: Randomization. PEV: Primary endpoint visit. EOS: End of study.

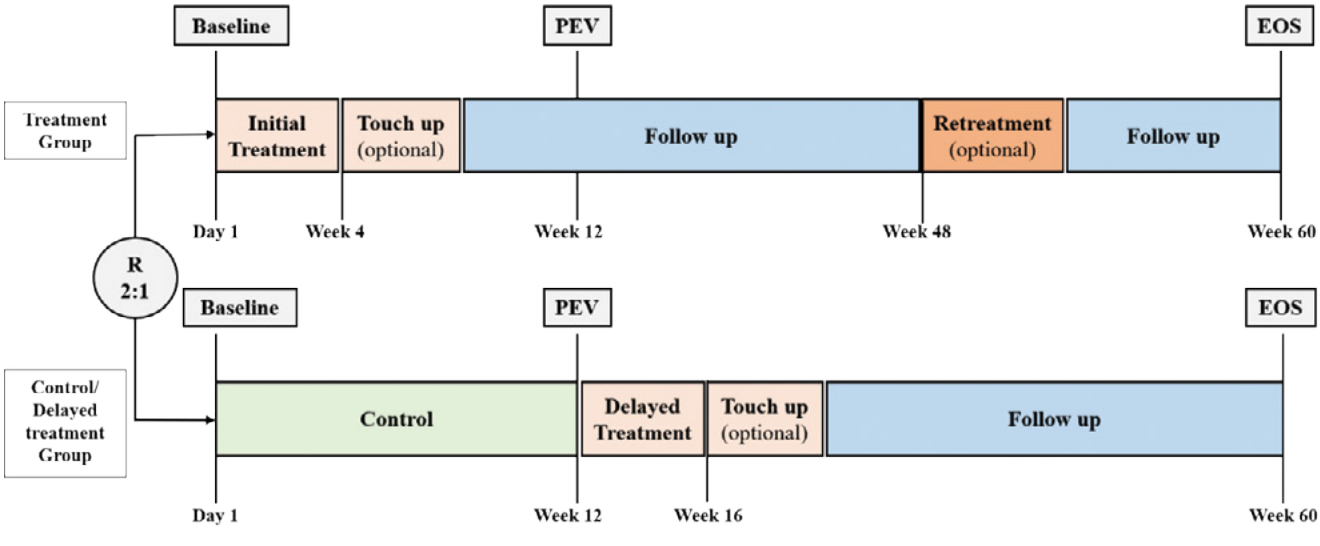


FIGURE 2. Patient disposition.

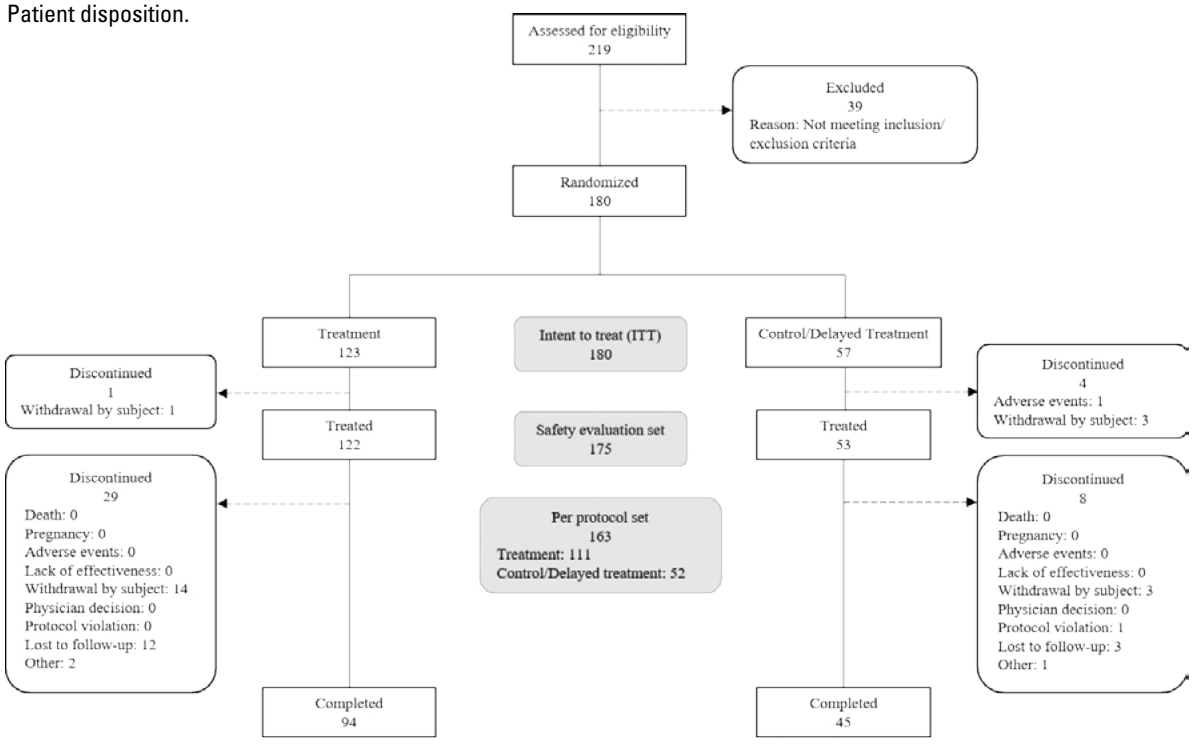


TABLE 1.

Demographic and Other Baseline Characteristics			
	Treatment (N=123)	Control/DT (N=57)	Total (N=180)
Sex, (n [%])			
Male	21 (17.1)	13 (22.8)	34 (18.9)
Female	102 (82.9)	44 (77.2)	146 (81.1)
Age [years]			
Mean (SD)	55.5 (7.3)	55.0 (6.6)	55.3 (7.1)
Ethnicity (n [%])			
Hispanic or Latino	22 (17.9)	9 (15.8)	31 (17.2)
Not Hispanic or Latino	101 (82.1)	48 (84.2)	149 (82.8)
Race (n [%])			
White	103 (83.7)	42 (73.7)	145 (80.6)
Asian	5 (4.1)	5 (8.8)	10 (5.6)
Black or African American	14 (11.4)	10 (17.5)	24 (13.3)
American Indian or Alaska Native	1 (0.8)	0 (0.0)	1 (0.6)
Fitzpatrick skin type (n [%])			
I – III	77 (62.6)	32 (56.1)	109 (60.6)
IV – VI	46 (37.4)	25 (43.9)	71 (39.4)
MJAS score by blinded rater			
Left jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)
Right jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)

DT= delayed treatment; SD = standard deviation, n = number of observations, N = number of patients; MJAS = Merz Jawline Assessment Scale.
Note: More than one response was allowed for race.

of hyaluronic acid products within 12 months prior to randomization.

Treatment

Patients were randomized (1:1) to receive CaHA (+) treatment in the jawline area with either needle (27 gauge, ¾") or cannula (27 gauge, 1.6") at baseline. The injection method assigned at baseline was maintained if patients received a touch-up and/or re-treatment. The injection techniques used were a combination of linear-threading/tunneling, serial puncture and fanning, and linear-threading/tunneling. In all three treated anatomical locations (ie, angle/ramus, mid-body, and anterior), injection at multiple depths was allowed (ie, subdermal and/or supraperiosteal). The maximum volume of CaHA (+) per jawline side was limited to 3 mL during initial treatment and no more than 1.5 mL per jawline side during touch-up. At retreatment, the maximum volume of CaHA (+) per jawline side was limited to 3 mL.

Outcomes

Primary effectiveness was assessed on the MJAS by blinded raters. The 5-point MJAS ranges from grade 0 (a continuous jawline contour and no loss of volume) to grade 4 (an extreme loss of jawline contour and loss of jawline volume). Prior to study initiation, the MJAS was validated in a live setting (ie, 2 sessions, 3-weeks apart) by board-certified facial plastic surgeons and dermatologists who rated male and female volunteers with varying jawline severities, Fitzpatrick skin types, and ages. All raters exceeded the minimum weighted Kappa point estimate of ≥0.70 for the intra- and inter-rater reliability, demonstrating the reliability of the MJAS. All blinded raters were qualified using the same criteria as used for MJAS validation before rating study patients.

The primary effectiveness endpoint was the comparison of responder rates between the treatment group and the untreated control group at week 12, according to the MJAS, as assessed live by the blinded rater. Treatment response was defined as a 1-point or greater improvement on both jawlines compared to baseline. Secondary and other endpoint assessments at week 12 included: FACE-Q™ Satisfaction with Lower Face and Jawline; patient and treating investigator ratings on the Global Aesthetic Improvement Scale (GAIS); independent panel review (IPR) responder rates according to the MJAS as assessed by three blinded raters in photographs (response defined as ≥1-point improvement on both jawlines by at least 2 raters), and FACE-Q™ Patient-perceived Age Visual Analogue Scale (VAS). Retention of treatment response was also assessed at 48 weeks post-treatment.

Safety assessments included investigator-reported adverse events (AEs) over a 60-week period and patient-reported common treatment responses (CTRs) recorded in an electronic diary for 28 days after each treatment session.

Statistical Analysis

Two hypothesis tests for the primary endpoint were performed in sequential order: 1) a binomial test was used to demonstrate at least 50% of treated patients were responders (H_{01}: $P_{treatment} \leq 50\%$ vs H_{11}: $P_{treatment} > 50\%$), and 2) the Fisher's exact test was used to compare the treatment group with the control group (H_{02}: $P_{treatment} \leq P_{control}$ vs H_{12}: $P_{treatment} > P_{control}$). Each hypothesis test was a one-sided test, at a significance level of 0.025. Secondary and other endpoints, as well as safety, were descriptively summarized. Additionally, subgroup analysis by sex and Fitzpatrick skin types were performed. The SAS® software package (SAS Institute, Cary, NC, USA) was used.

RESULTS

Patients

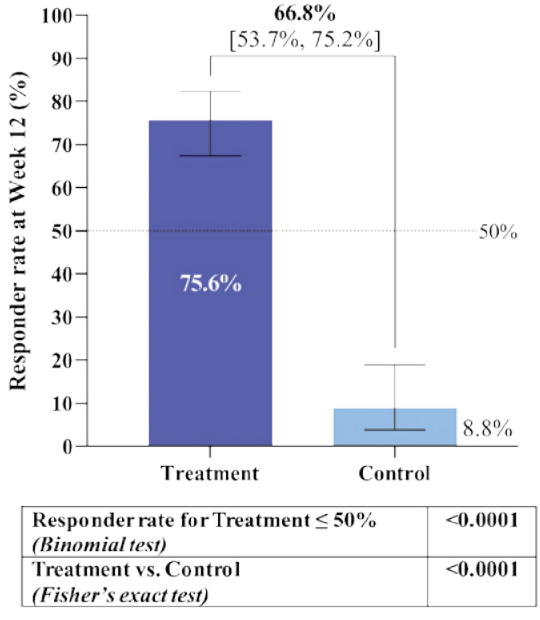
A total of 219 patients were screened with 180 patients being enrolled and randomized (123 to treatment and 57 to control/delayed treatment; Figure 2) including patients of all Fitzpatrick skin types, both males and females, and patients of various ages and races. The majority (81.1%) of patients were female, self-identified as White (80.6%) and mean (SD) age was 55.3 (7.1) years (Table 1). Regarding Fitzpatrick skin type categories, 60.6% of patients had skin types I, II, or III, and 39.4% had skin types IV, V, or VI. For baseline severity MJAS scores, 55% of patients had a score of 2 (moderate) and 45% had a score of 3 (severe); all patients had the same baseline score on both sides of their jawlines.

Treatment

A total of 175/180 randomized patients received treatment (Figure 2) with either needle (88/175 patients) or cannula (87/175 patients). The median injection volume for each side of the jawline was 1.80 mL. Among patients receiving a touch-up (132/175, 75.4%), the median volume injected was 1.10 mL in the right jawline and 1.25 mL in the left jawline. In treatment-group patients eligible for re-treatment at week 48 (76/122, 62.3%), median re-treatment injection volumes were 1.40 mL for the right jawline and 1.50 mL for the left jawline. No patient was injected with more than 3 mL of CaHA (+) per jawline per treatment session. No clinically significant trends were identified when considering the volume injected during each injection cycle or between the treatment and delayed-treatment groups.

The most commonly used injection techniques were serial puncture when injecting with a needle and linear-threading/tunneling when injecting with a cannula. The most common injection depth was subdermal and patients were frequently injected at multiple depths. The median number of injection points per jawline was 3 for all three treatment sessions, with a higher number of injection points when a needle was used, as expected.

FIGURE 3. Merz Jawline Assessment Scale (MJAS) responder rate at week 12 as assessed live by a blinded rater among the intent-to-treat population. Treatment response is defined as ≥ 1-point improvement on both jawlines compared to baseline. Bars represent confidence intervals (CI). Wilson CIs are calculated for responder rates. Newcombe CIs are calculated for responder rate differences.



Responder rate for Treatment ≤ 50% *(Binomial test)*	<0.0001
Treatment vs. Control *(Fisher's exact test)*	<0.0001

Effectiveness

At week 12, the majority of patients (75.6%) in the treatment group showed a ≥ 1-point improvement on the MJAS in both jawlines when compared to baseline. The responder rates were significantly greater than 50% in the treatment group (P<0.0001), meeting the threshold for clinical effectiveness (Figure 3). In contrast, only 8.8% of patients in the control group were responders.

A statistically significant difference of 66.8% (P<0.0001) was demonstrated between the response rates in the treatment and the control groups. The 95% confidence interval (CI) for the difference in response rates was [53.7%, 75.2%], showing a lower bound greater than zero. Representative before and after treatment photographs are shown in Figure 4.

Similar results were also observed when stratifying MJAS responder rates at week 12 by Fitzpatrick skin type categories (difference in response rates between treatment and control group [95% CI]: I–III = 65.2% [47.5%, 75.1%] and IV–VI = 70.6% [48.2%, 82.0%]) and sex (females = 70.6% [56.1%, 79.0%] and males = 51.3% [17.0%, 70.8%]) with lower bounds of CIs greater than zero in both skin type categories and in both males and females.

Regarding durability, 76/113 (67.3%) patients who responded to treatment 12 weeks after initial injection also retained response 48 weeks after initial treatment. A small subset of patients who were responders at week 12 and did not receive re-treatment, retained response up to 60 weeks post-initial treatment (7/17, 41.2%).

For the FACE-Q Satisfaction with Lower Face and Jawline module, the mean (SD) Rasch-transformed scores in patients randomized to the treatment group increased from 21.5 (18.9) at baseline to 75.2 (22.3) at week 12. The mean (SD) change from baseline to week 12 was 53.9 (25.7), and the respective 95% CI of [49.2, 58.7] excluded zero. Overall, the improvement in mean Rasch-transformed scores indicated a better outcome, with patients reporting being more satisfied with how prominent and how sculpted their jawline looked, how their jawline looked in profile, how nice their lower face looked, and how smooth their faced looked.

All but one (99.1%) patient in the treatment group showed some level of improvement on the GAIS, as determined by the treating investigator (Figure 5). The remaining patient was reported to show no change in the treating investigator's judgement. The

FIGURE 4. Representative photographs of the jawline before (left) and after (right) treatment with CaHA (+). Lateral (top) and oblique (bottom) photographs are provided for each patient.

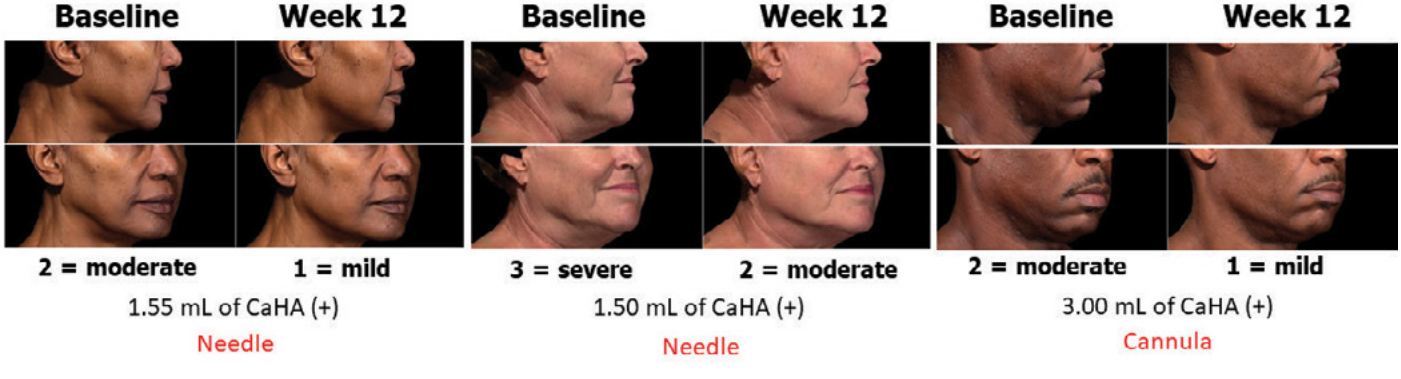
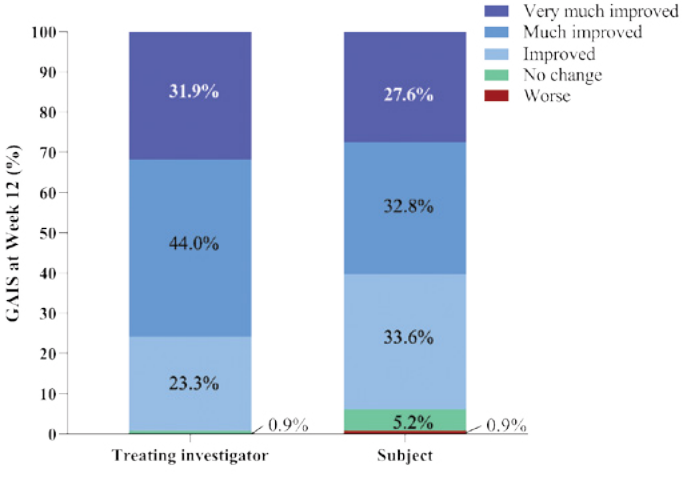


FIGURE 5. Treating investigator and patient Global Aesthetic Improvement Scores (GAIS) at week 12 among the intent-to-treat population. GAIS was assessed relative to baseline photographs.



majority of patients (94.0%) in the treatment group self-reported some level of improvement on the GAIS (Figure 5). Six (5.2%) patients reported seeing no change, and 1 (0.9%) patient reported looking worse when compared to baseline photographs.
At least two blinded IPRs assessed that 53 (47.7%) of 111 patients in the treatment group and 4 (8.2%) of 49 patients in the control group showed a treatment response of ≥1-point change on both jawlines, showing a difference of 39.6% [25.3%, 50.0%] between groups.

Furthermore, according to FACE-Q VAS, patients in the treatment group self-reported on average looking younger by approximately 3 years at week 12 when compared to baseline.

Safety

CaHA (+) was found to be tolerable and safe at up to three treatment sessions, and during the study's long-term follow-up period. Investigators reported at least one treatment emergent adverse event (TEAE) in 74/175 (42.3%) patients exposed to treatment. Three (3/175, 1.7%) patients had serious TEAEs that were unrelated to the treatment device. No TEAEs leading to study discontinuation were reported.

Overall, 46/175 (26.3%) patients had at least one TEAE that was deemed to be related to treatment by the investigator (Table 2). The most frequently reported treatment-related TEAEs were administration site conditions that were mild, lasted less than 15 days, and resolved without sequelae. Importantly, only one patient injected with needle had treatment-related TEAEs that were severe: injection site bruising (1 event, lasting 16 days) and injection site edema (1 event, lasting 16 days), and both events resolved. There were no treatment-related serious adverse events (SAEs). Only one patient (0.8%) had one mild treatment-related TEAE with unknown outcome due to being lost to follow-up.

TABLE 2.

Treatment-Related Treatment Emergent Adverse Events, Safety Set		
	Total (N=175)	
Preferred Term	n	(%)
Patients with at least one treatment-related TEAE	46	(26.3)
Injection site mass	19	(10.9)
Injection site bruising	12	(6.9)
Injection site pain	12	(6.9)
Injection site nodule	6	(3.4)
Injection site edema	6	(3.4)
Injection site swelling	6	(3.4)
Injection site hemorrhage	4	(2.3)
Injection site erythema	3	(1.7)
Injection site induration	3	(1.7)
Injection site inflammation	3	(1.7)
Device dislocation	2	(1.1)
Injection site extravasation	2	(1.1)
Product distribution issue	2	(1.1)
Ear pain	1	(0.6)
Injection site discomfort	1	(0.6)
Injection site rash	1	(0.6)

N = number of patients exposed, TEAE = treatment emergent adverse event. Treatment-related TEAEs are defined as any adverse event with onset date on or after date of initial treatment related to injection procedure or related to CaHA (+).

Rates of treatment-related TEAEs were comparable between female (37/144, 25.7%) and male (9/31, 29.0%) subgroups.
Rates of patients with treatment-related TEAEs were equally similar and favorable for Fitzpatrick skin type category I to III when compared to skin type category IV to VI (I–III = 30/109, 27.5% and IV–VI = 16/66, 24.2%).

Common treatment responses (CTRs) were self-reported by patients in electronic diaries for 28 days post-treatment. After initial treatment, the majority of patients reported CTRs (eg, swelling, firmness, lumps/bumps, bruising, and discomfort/pain) that were mild (81/175, 46.3%) to moderate (81/175, 46.3%) in nature and had a duration of 14 days or less (1–3 days: 22/175, 12.6%; 4–7 days: 68/175, 38.9%; and 8–14 days: 46/175, 26.3%). CTRs reported in the study were similar for all three diary cycles (initial treatment, touch up, and retreatment), although incidences of subjects reporting at least 1 CTR tended to be lower after touch-up (77.8%) and re-treatment when compared to initial treatment.

DISCUSSION

CaHA (+) demonstrated clinically and statistically significant sustained improvements in the contour of the jawline. This objective measure was further supported by multiple patient- and investigator-reported endpoints demonstrating aesthetic improvements following treatment.

The study population, which included male and female patients of various ages and races and all Fitzpatrick skin types, was representative of the diverse group of patients that typically receives aesthetic treatments in the facial region.[13]

Overall, the injection volumes utilized lead to the desired aesthetic outcome and were in line with standard clinical practice.[4,12,14-15]

At week 12, responder rates were calculated according to the MJAS as assessed by a blinded rater. Treatment response was defined as a ≥1-point improvement on both jawlines compared to baseline; this metric of improvement is a common criterion for aesthetic-medicine clinical trials, indicating demonstration of clinically relevant results.[16-20] The treatment response rate for the CaHA (+) group was 75.6%, exceeding the targeted margin of 50% (P<0.0001). In contrast, 8.8% of patients in the untreated control group were assessed as responders at week 12. The difference between the response rates in the treated and untreated groups at week 12 was statistically significant (66.8%, P<0.0001). Overall, comparable results were observed when stratifying results by Fitzpatrick skin type categories (I–III vs IV–VI) and sex (females vs males).

These findings demonstrate that CaHA (+) is an effective treatment for improving the contour of the jawline area. All patients categorized as responders at week 12 were assessed for duration of treatment effectiveness with the majority of patients demonstrating retention of treatment response at 48 weeks. Additionally, a small subset of patients who did not receive re-treatment retained treatment response up to 60 weeks post-treatment.

All results from the secondary endpoints related to patient- and investigator-reported assessments (eg, FACE-Q Satisfaction with Lower Face and Jawline and investigator and patient GAIS) successfully support the primary endpoint indicating that CaHA (+) is an effective treatment for improving contour of the jawline area.

Overall, study findings indicate improvements reported by investigators and patients 12 weeks after treatment with CaHA (+) (ie, when patients were expected to experience maximum treatment benefit), and additionally support the sustained effect of CaHA (+) treatment for up to 48 weeks when injected in the jawline.

This CaHA (+) pivotal study demonstrated a favorable safety profile, with no treatment-related SAEs and no unexpected or atypical events reported. Treatment-related adverse events consisted primarily of administration site conditions, were generally mild to moderate in intensity, lasted for less than 15 days, and mainly resolved prior to study end. Findings from the patient's CTR diary were in line with expectations for injection procedures with dermal fillers in the face and the expected safety profile of CaHA (+) from a patient self-reporting perspective.[16-20] In general, safety findings were similar in incidence, severity, and duration when stratified by Fitzpatrick skin type categories (I–III vs IV–VI) and sex (females vs males). These findings demonstrate that injected CaHA (+) is a safe and well tolerated treatment option to improve jawline contour.

CONCLUSION

These study findings demonstrate that CaHA (+) is a safe and effective treatment for improving moderate to severe loss of jawline contour and have substantiated its FDA-approval for this indication.

DISCLOSURES

This research was supported and funded by Merz North America, Inc.

Dr. Cohen has served as a consultant, clinical investigator, and member of the Global Key Opinion Leader Network for Merz Aesthetics. Dr. Green is a consultant, clinical investigator, and speaker for Merz Aesthetics. Dr. Scher, Dr. Verma, and Dr. Odena are employees of Merz North America, Inc. Dr. Dakovic is an employee of Merz Pharmaceuticals GmbH.

REFERENCES

1. Loghem JV, Yutskovskaya YA, Philip Werschler W. Calcium hydroxylapatite: over a decade of clinical experience. *J Clin Aesthet Dermatol.* 2015;8(1):38-49.
2. Lorenc ZP, Lee JC. Composite volumization of the aging face: supra-periosteal space as the foundation for optimal facial rejuvenation. *J Drugs Dermatol.* 2016;15(9):1136-41.
3. Pavicic T, Few JW, Huber-Vorländer J. A novel, multistep, combination facial rejuvenation procedure for treatment of the whole face with incobotulinumtoxinA, and two dermal fillers- calcium hydroxylapatite and a monophasic, polydensified hyaluronic acid filler. *J Drugs Dermatol.* 2013;12(9):978-84.
4. Dallara JM, Baspeyras M, Bui P, et al. Calcium hydroxylapatite for jawline rejuvenation: consensus recommendations. *J Cosmet Dermatol.* 2014;13(1):3-14.
5. Sclafani AP, Kwak E. Alternative management of the aging jawline and neck. *Facial Plast Surg.* 2005;21(1):47-54.
6. Graivier MH, Bass LS, Busso M, et al. Calcium hydroxylapatite (Radiesse) for correction of the mid- and lower face: consensus recommendations. *Plast Reconstr Surg.* 2007;120(6 Suppl):55s-66s.
7. Dayan SH, Lieberman E, Larimer K. High-volume calcium hydroxylapatite filler to the lower one-third of the face. *Arch Facial Plast Surg.* 2009;11(2):145-7.
8. Hamilton D. Calcium Hydroxylapatite for Augmentation of the Posterior Mandibular Angle in Men. *Cosmetic Dermatology.* 2009;22(9):474-78.
9. Bartus CL, Sattler G, Hanke CW. The tower technique: a novel technique for the injection of hyaluronic acid fillers. *J Drugs Dermatol.* 2011;10(11):1277-80.
10. Braz A, Humphrey S, Weinkle S, et al. Lower face: clinical anatomy and regional approaches with injectable fillers. *Plast Reconstr Surg.* 2015;136(5 Suppl):235S-57S.
11. Buckingham ED, Glasgold R, Kontis T, et al. Volume rejuvenation of the facial upper third. *Facial Plast Surg.* 2015;31(1):43-54.

12. Baspeyras M, Dallara JM, Cartier H, et al. Restoring jawline contour with calcium hydroxylapatite: A prospective, observational study. *J Cosmet Dermatol*. 2017;16(3):342-7.
13. The American Society for Aesthetic Plastic Surgery: Cosmetic Surgery National Data Bank Statistics; Available at: https://www.surgery.org/sites/default/files/ASAPS-Stats2016.pdf. Accessed November 2016.
14. Juhász MLW, Marmur ES. Examining the efficacy of calcium hydroxylapatite filler with integral lidocaine in correcting volume loss of the jawline-a pilot study. *Dermatol Surg*. 2018 Aug;44(8):1084-1093.
15. Moradi A, Shirazi A, David R. Nonsurgical chin and jawline augmentation using calcium hydroxylapatite and hyaluronic acid fillers. *Facial Plast Surg*. 2019 Apr;35(2):140-148.
16. Juvéderm Vollure XC [Instructions for use]. Irvine, CA: Allergan; 2019.
17. Juvéderm Volbella XC [Instructions for use]. Irvine, CA: Allergan; 2016.
18. Juvéderm Voluma XC [Instructions for use]. Irvine, CA: Allergan; 2013.
19. Restylane Lyft with Lidocaine [Instructions for use]. Fort Worth, TX: Galderma Laboratories; 2018.
20. Restylane-L Instructions for Use [Instructions for use]. Fort Worth, TX: Galderma Laboratories; 2016.

AUTHOR CORRESPONDENCE

Gemma Odena PhD
E-mail:..... gemma.odena@merz.com

NOW AVAILABLE!

Algorithm for Pre-/Post-Procedure Measures for Facial Nonenergy-based and Injectable Skin Treatments

Available Now in the JDD Supplement Library
www.jddonline.com/supplement_library

Swiss American, LLC supported the research and development of the algorithm with an unrestricted educational grant. This supplement to the *Journal of Drugs in Dermatology* is funded by International Dermatology Educational Foundation.

doi:10.36849/JDD.6166

November 2021 1239 Volume 20 • Issue 11

Copyright © 2021

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Aminolevulinic Acid 20% Solution Combined With Photodynamic Therapy for Treatment of Actinic Keratoses: A Review

Joe Gorelick MSN FNP-C,[a] Scott Freeman MCMS PA-C[b]

[a]California Skin Institute, San Jose, CA
[b]Advanced Dermatology, St. Petersburg, FL

ABSTRACT

Actinic keratoses (AK) are lesions with potential to transform into nonmelanoma skin cancers. Numerous methods are available for treatment of AK. Here, we review clinical trial data on the use of photodynamic treatment combined with the sensitizing agent aminolevulinic acid 20% solution (ALA-PDT) for AK management. Although treatment guidelines for AK vary in their specific recommendations, efficacy of ALA-PDT is considered comparable or better relative to other FDA-approved treatments for AK. It is generally well tolerated and has a very acceptable long-term safety profile. ALA-PDT is typically recommended for patients who have multiple AKs and is associated with improved cosmetic outcomes compared with cryotherapy. Patients who undergo treatment with ALA-PDT should receive thorough education regarding the risks and benefits of treatment, the treatment regimen and the importance of adhering to it, how to manage local reactions, and signs and symptoms that warrant further evaluation.

J Drugs Dermatol. 2021;20(11):1239-1244. doi:10.36849/JDD.6166

INTRODUCTION

Actinic keratoses (AK) are dysplastic epidermal lesions resulting from long-term sun exposure that have potential to progress to nonmelanoma skin cancer (NMSC), particularly squamous cell carcinoma (SCC).[1,2] They are a manifestation of abnormal keratinocyte proliferation and differentiation.[3]

AKs may be considered visible evidence of a photo-damaged field with changes predisposing the patient to development of NMSC.[4] However, AKs may also spontaneously resolve or remain stable without malignant transformation.[3] In one study of 169 patients with 7784 AKs, 5.6% of patients progressed to develop SCC or basal cell carcinoma (BCC) within 5 years.[4,5] Another study predicted that patients with an average of 7.7 AKs had a 10% risk of developing SCC within 10 years.[3] Further, roughly two-thirds of primary SCCs, one-third of primary BCCs, and 60% to 80% of invasive SCCs arose in AK lesions.[4,5]

The prevalence of AK varies from 6% to 60% among populations and appears to be increasing.[2] Factors increasing risk for AK include age, skin phototype, lifestyle, and occupation (eg, working outdoors), geographical location, history of skin cancer, and immunosuppressed status.[2] Development of AK is more likely in patients whose skin burns easily (eg, phototype I) compared with those who rarely burn (eg, phototype VI).[6] They primarily occur on areas of skin that experience chronic sun exposure, particularly the head and neck, followed by the upper extremities.[3] The total direct costs associated with AK in 2004 were estimated at $1.2 billion, with the majority of these costs resulting from outpatient visits to health care providers for treatment.[4]

Although some AKs are associated with sensations of itching or tenderness, most are generally asymptomatic.[3] Patients often describe the lesions as rough "sandpaper"-like patches. AKs are graded using a 3-point scale: grade 1 lesions are visible and palpable, grade 2 lesions are usually red and scaly, and grade 3 lesions are thicker, hyperkeratotic lesions that can be difficult to differentiate from early SCCs.[3] Presence of a single lesion may be associated with development of multiple lesions in the future.[3] When multiple AKs are present, they are considered to be evidence of "field change," ie, an area of skin with extensive actinic damage.[3]

Overview of Treatment Options for Actinic Keratoses

The goals of AK treatment are to eliminate existing AKs and minimize risk of recurrence and progression to SCC.[2] Available treatment options include photodynamic therapy (PDT) with photosensitizing agents; topical agents such as 5-fluorouracil, imiquimod, diclofenac, and topical retinoids; cryosurgery;

curettage; laser therapy; and systemic therapy (eg, systemic retinoids). Light sources for PDT include red- and blue-spectrum; red narrow-spectrum sources require less illumination time and may be associated with a higher rate of response.[3] The addition of photosensitizing agents to PDT induces apoptosis and necrosis of target tissue. Factors that influence treatment selection include efficacy, potential for side effects, number of lesions, grade, location of lesions, response to previous therapy, cosmetic impact, regimen flexibility and convenience, availability, patient preference, and cost.[1,3]

Treatments can be directed to specific lesions or the entire "field." When isolated lesions are treated, for example, with cryotherapy, underlying subclinical actinic damage may not be visualized. By using field therapy techniques, both clinical and subclinical lesions receive treatment, achieving more comprehensive clearance of actinic damage.

Neither surgical excision nor biopsy is routinely performed.[7] Biopsy may be appropriate if NMSC or other conditions such as Bowen's disease cannot be ruled out with clinical evaluation and dermoscopy.[8]

Treatment Guidelines for AK

Several treatment guidelines for treatment of AK have been published, including Canadian, European, British, Italian, and Swiss guidelines.[3,7-10] Additional treatment guidelines are available for patients at higher risk of SCC.[11] There is significant heterogeneity among the organization and structure of available guidelines. For example, Canadian guidelines recommend surgical excision or curettage for isolated AKs and state that topical treatments including 5-FU, imiquimod, or ingenol mebutate (discontinued in 2020[12]) may be used for isolated or clustered AKs (4 or more), whereas PDT or other field-directed therapies are recommended for clustered AKs.[7] British guidelines provide an "A" recommendation for several therapies: diclofenac, cryotherapy, PDT with either 5-aminolevulinic acid or its methyl ester (methyl aminolevulinate; MAL) as a photosensitizing agent, 5-FU, imiquimod, or ingenol mebutate. Treatments with a "B" recommendation include laser resurfacing, chemical peels, dermabrasion, and other topical agents.[3,13] Tirbanibulin—approved by the FDA for AK treatment in December 2020—is not yet included in treatment guidelines.[14]

Some guidelines suggest that treating AK is not always required; however, experts are divided on this issue.[3] Guidelines from the British Association of Dermatologists indicate that patient preference and clinical circumstances (eg, extent, duration, symptoms, and risks for skin cancer) should be considered when determining whether to treat AK.[3] In contrast, Canadian treatment guidelines state that AKs should be treated due to their chance of progression to SCC and because they can be difficult to distinguish from early SCC.[7] The Progressing Evidence in AK (PEAK) Working Group recommends treatment of AK by default, especially in patients at increased risk of NMSC,[2] although direct evidence that AK treatment prevents progression to NMSC is lacking.[2] AK lesions that progress to SCC following treatment may have been SCC lesions that were initially diagnosed as AK and had a deep component that persisted through treatment.[15] In the clinical setting, in light of the potential for malignancy, most identified AKs are treated.

A comprehensive review of available guidelines is beyond the scope of this article. In general, cryotherapy is the most widely recommended treatment for isolated AKs, whereas field therapies (5-FU, imiquimod, PDT with a photosensitizing agent, and likely tirbanibulin when added to guidelines) are recommended for multiple AKs.[13] PDT for AK is considered highly effective, with efficacy at least comparable to other FDA-approved treatments. It is associated with improved cosmetic outcomes compared with cryotherapy.[16]

Aminolevulinic Acid 20% Solution Combined With Photodynamic Therapy (ALA-PDT)

Mechanism of Action of ALA-PDT

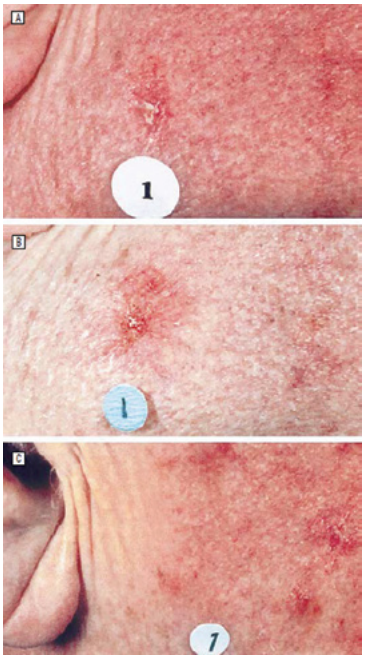
Due to its encouraging efficacy and safety profile, including favorable cosmetic outcomes, and field-directed nature, PDT with 5-aminolevulinic acid 20% solution as a photosensitizer (ALA-PDT) is often used in treatment of AK. 5-aminolevulinic acid is a prodrug that is absorbed and metabolized to protoporphyrin IX (PpIX). When PDT of the appropriate wavelength is applied, a cytotoxic reaction produces reactive oxygen species (ROS), resulting in apoptosis and necrosis of the treated lesion with minimal damage to untreated skin.[15,17]

Clinical Efficacy of ALA-PDT

Per US labeling, ALA-PDT combining 5-aminolevulinic acid 20% solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for photodynamic therapy (treatment) of minimally to moderately thick AKs of the face or scalp, or AKs of the upper extremities.[18] In several phase 3 or 4 clinical trials, ALA-PDT was highly effective for treatment of minimally to moderately thick AKs when used as directed (Table 1).[1,15,19,20] Initial trials investigated safety and efficacy of ALA-PDT for the treatment of AK on the face and scalp, while more recent trials have addressed AK on the upper extremities.[15]

In a phase 3 multicenter trial conducted by Piacquadio et al, 243 patients with 4 to 15 AK lesions on the face or scalp were randomized to treatment with PDT and either ALA or vehicle.[19] At 8 weeks after treatment, ≥75% of AK lesions were cleared in 77% of patients receiving ALA-PDT vs 18% receiving vehicle-PDT (P<0.001).[19] Complete response rates (100% clearance) at 8 weeks occurred in 66% of ALA-PDT treated patients vs 11% of vehicle-PDT treated patients (P <0.001).[19] Photographs from a

FIGURE 1. Case example from phase 3 trial of 20% aminolevulinic acid solution followed by photodynamic therapy using blue light. (A) Pretreatment, (B) 24 hours posttreatment, (C) 8 weeks posttreatment. Reproduced with permission from Piacquadio, et al. *Arch Dermatol.* 2004;140:41–46.



case example are reproduced as Figure 1.

Tschen et al, conducted a phase 4 open-label study of 110 patients with 6 to 12 AKs on the face or scalp.[20] Patients were treated with ALA-PDT and followed with monthly visits for 12 months. Any treated lesions that remained at month 2 were retreated with ALA-PDT; 66% of these patients received a second treatment at month 2. Lesions that did not respond to treatment were biopsied at month 3.[20] Seventy-six percent (76%) of target lesions were completely cleared at month 1 and 72% at month 2; complete clearance peaked at month 4 at 86% of lesions and then declined gradually to 78% of all lesions at month 12. The percent of patients with complete clearance (100% of target lesions) was 67% at month 3 and declined to 40% at month 12. Beginning at month 6, clearance rates were slightly higher in patients with skin types I and II compared with skin types III and IV.[20] The percentage of lesions that cleared was similar for grade 1 and grade 2 lesions.

Jiang et al, investigated treatment with ALA-PDT or vehicle-PDT in patients with 4 to 15 grade 1 or 2 AKs on one upper extremity.[15] Among patients who received a second treatment, the mean AK lesion clearance rate in patients who received ALA was 69.1% at week 12, compared with 29.9% in vehicle-treated patients (P<0.0001).[15] The number of patients who experienced complete clearance was also significantly greater in those who received ALA vs vehicle (P=0.0001).[15]

In a post hoc analysis of a phase 3 study of 269 patients with 4–15 grade 1–2 AKs on an upper extremity, patients were treated with ALA-PDT or vehicle-PDT, applied twice. Treatment was also applied at week 8 if lesions were present in the treatment area.[1] At weeks 8 and 12, AK clearance rates were significantly greater in patients who received ALA-PDT vs vehicle-PDT. At week 12, the clearance rates were 80.6% in those receiving ALA-PDT and 45.5% in those receiving vehicle-PDT. Cumulative disease area cleared was also greater in those who received ALA-PDT. Results were similar across all baseline lesion sizes.[1]

Efficacy in High-Risk Patients

Piacquadio conducted a phase 2 trial in patients at high risk for progression to NMSC. Patients had 4–15 facial AKs grade 1–3 and had been previously been treated for NMSC in a sun-exposed area.[21] A total of 166 patients underwent cryotherapy at screening and then were randomized to treatment with ALA-PDT or vehicle-PDT applied 2 times (baseline and week 4) or 3 times (baseline, week 4, and week 24).[21] Compared with vehicle-PDT treatment, ALA-PDT treatment performed 3 times significantly reduced the rate of new and recurrent AKs at 52 weeks.[21] Complete clearance rates at week 52 were 36% for ALA 2x, 37.5% for ALA 3x, and 18.9% for vehicle ($P \leq 0.01$ for each ALA treatment vs vehicle).[21]

Clinical Safety

The safety profile of ALA-PDT includes consideration of the immediate and short-term effects of PDT, ALA, and ALA-PDT as well as potential long-term effects of treatment, particularly the development of NMSC. However, long-term NMSC rates have only been reported in more recent trials.

Early-Onset Side Effects

Common early-onset side effects of PDT include pain and local skin reactions (erythema, edema, desquamation, and pustules). These effects often occur within hours or days of exposure to PDT and can negatively impact patient satisfaction.[17]

In the trial of patients with AK on the face or scalp by Piacquadio et al, adverse events (AEs) were similar in patients treated with either ALA or vehicle.[19] The overwhelming majority of AEs (92%) were mild or moderate; 97% of AEs were considered unrelated to ALA treatment. The most common AEs related to treatment were headache, dry skin, and conjunctivitis.[19] Patient discomfort due to PDT (eg, stinging and burning during PDT treatment) was reported by >90% of patients receiving ALA-PDT; only 28% reported any discomfort after 24 hours. Other common local responses included erythema, edema, crusting, pruritis, and scaling.[19] Rates of SCC or BCC diagnosis following treatment were not reported.

In the open-label study reported by Tschen et al, AEs associated with PDT were common immediately after treatment; 95% of

TABLE 1.

Summary of Efficacy Results of ALA Phase 3 and 4 Trials			
Endpoint	**ALA-PDT**	**VEH-PDT**	***P* value vs VEH**
Patients with upper extremity AKs[1]			
Mean clearance rate of treated upper extremity AKs at week 8	67.3	37.2	<0.0001
Mean clearance rate of treated upper extremity AKs at week 12	80.6	45.5	<0.0001
Percent of patients with cumulative disease area cleared at week 8	67.8	37.2	<0.0001
Percent of patients with cumulative disease area cleared at week 12	82.4	42.6	<0.0001
Patients with upper extremity AKs[15]			
Mean clearance rate of treated upper extremity AKs at week 8	53.4	26.3	<0.0001
Mean clearance rate of treated upper extremity AKs at week 12	69.1	29.9	<0.0001
Percent of patients with cumulative disease area cleared at week 8	25.9	9.0	<0.0001
Percent of patients with cumulative disease area cleared at week 12	31.1	12.7	<0.0001
Patients with face and scalp AKs[19]			
Percent of patients with ≥75% clearance at week 8	77	18	<0.001
Percent of patients with ≥75% clearance at week 12	89	13	<0.001
Percent of patients with complete disease area cleared at week 8	66	11	<0.001
Percent of patients with complete disease area cleared at week 12	73	8	<0.001
High-risk patients with facial AK[21]			
Lesion recurrent rate at week 52	ALA 2x: 7.7 ALA 3x: 6.1	15.5	0.0004 for ALA 2x <0.0001 for ALA 3x
Mean duration of response, weeks	ALA 2x: 35.9 ALA 3x: 33.3	25.9	NR

AK, actinic keratoses; ALA, aminolevulinic acid; NR, not reported; PDT, photodynamic therapy; VEH, vehicle.

patients experienced erythema, and 79% experienced edema.[20] ALA treatment increased the rate of stinging/burning from 16% at baseline to 64% during the incubation period following application and prior to light treatment; 96% of patients reported stinging/burning during light treatment. These side effects all subsided at follow-up visits, when rates were lower than those observed at baseline.[20] The AK recurrence rate was 24% (162/688); 139 were biopsied. Rates of SCC or BCC diagnosis among biopsied lesions were 7% and 0.7%.

In the upper extremity trial by Berman et al, ALA-PDT was generally well tolerated, and reactions to treatment were nonserious and resolved within several weeks. Compared with vehicle pretreatment, ALA pretreatment increased the incidence and severity of side effects associated with PDT, including erythema, edema, stinging/burning, scaling, dryness, and oozing/vesiculation/crusting. No clinically significant AEs were reported in either treatment group.[1] Similar results were found by Jiang et al; the incidence of erythema appeared more

TABLE 2.

Summary of Safety Results of ALA Phase 3 and 4 Trials		
Endpoint	**ALA-PDT**	**VEH-PDT**
Berman et al.—Patients with upper extremity AKs[1]		
Patients diagnosed with SCC	9 lesions in 7 patients	3 lesions in 3 patients
Patients diagnosed with BCC	0	4 lesions in 3 patients
Jiang et al.—patients with upper extremity AKs[15]		
Patients diagnosed with SCC	2	1
Patients diagnosed with BCC	NR	NR
High-risk patients with facial AK[21]		
Patients diagnosed with SCC	ALA 2x: 6 ALA 3x: 3	7
Patients diagnosed with BCC	ALA 2x: 4 ALA 3x: 2	5

AK, actinic keratoses; ALA, aminolevulinic acid; BCC, basal cell carcinoma; NR, not reported; PDT, photodynamic therapy; SCC, squamous cell carcinoma; VEH, vehicle.

frequent in patients treated with ALA than vehicle.[15]

Late-Onset Adverse Events

PDT has been associated with hyperpigmentation and scarring in rare cases; however, the most concerning potential AE is development of NMSC, also a rare event.[17] Because patients with AK are already predisposed to NMSC, it is difficult to associate PDT with NMSC pathogenesis. However, PDT could potentially mediate development of NMSC via generation of ROS or immunosuppressive effects.[17] Therefore, careful assessment of NMSC rates in patients receiving PDT treatment is warranted (Table 2).

In the upper extremity trial by Berman et al, 16 skin carcinomas were diagnosed; 9 SCCs were diagnosed in 7 patients receiving ALA-PDT (all with a prior history of SCC), and 3 SCCs were diagnosed in patients receiving vehicle-PDT.[1] Three BCCs were diagnosed in patients who received vehicle-PDT.[1] In the trial by Jiang et al, new SCC developed in 2 patients who received ALA and one who received vehicle; all had a previous history of SCC.[15] In the study of high-risk patients conducted by Piacquadio et al, there were a total of 27 NMSCs reported during follow-up; the rate was significantly lower in patients who received ALA-PDT 3 times compared with patients who received vehicle.[21]

Patient Education for ALA-PDT

Patient education related to the use of ALA-PDT for the treatment of AK should begin with a discussion of the risks and benefits of treating AK. Patients with AK should be educated that they have evidence of sun damage and are at risk for development of NMSC. Regardless of treatment decisions, education should include information about signs and symptoms that require further evaluation, including bleeding or painful lesions, and lesions that grow or begin to protrude.[3] Risks and benefits of available treatment options should also be discussed.

Several barriers hinder use of field therapy with ALA-PDT, including the time needed to explain the treatment regimen, properly apply the treatment, address the immediate pain and inflammation, and ensure that patients adhere to requirements associated with the regimen.[4] Benefits of ALA-PDT include that it is more convenient and less invasive than surgery, is not associated with long-term side effects, and results in little to no scarring. Additionally, it avoids potential adherence issues that may arise with treatments applied exclusively by the patient.

If treatment with ALA-PDT is selected, it is important to educate patients about the regimen. ALA treatment must be applied prior to PDT treatment; the specific incubation time depends on the location. Patients should be advised that if they are unable to return for the PDT treatment during the appropriate period after applying the solution, they should avoid exposure of the photosensitized lesions to sunlight for at least 40 hours. Patients should also be advised to avoid medications that enhance the phototoxic reaction to PDT, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines.[18]

It is imperative that clinicians provide patients with comprehensive education regarding proper home care following ALA-PDT treatment. Patients must remain indoors and avoid all direct sunlight (even sitting by a window) for 36 hours. If patients must go outside, appropriate protective apparel such as a wide-brimmed hat, long-sleeved shirt, and gloves may be used to protect the skin from sunlight and other bright light; sunscreen will not be effective.[18] Patients should wash the treated area twice daily with a gentle cleanser and apply moisturizer 4 times daily. If the treated area is painful, patients may use nonprescription analgesics (ie, acetaminophen or ibuprofen) and apply ice packs for 5–10 minutes every few hours. Patients should be advised to expect redness and for the skin to feel dry and tight. Makeup may be used if desired once any crusting has healed. When patients go outdoors after the first 36 hours, they should use broad spectrum sunscreen that provides a physical barrier such as zinc oxide or titanium dioxide.[16]

CONCLUSION

ALA-PDT is effective and well tolerated for the treatment of AK located on the face, scalp, and upper extremities. Clinical trials have found dramatically improved rates of AK clearance following treatment with ALA-PDT compared with PDT applied with vehicle alone. Field therapy for AK with a treatment such as ALA-PDT is supported for patients with multiple AKs and may reduce the risk for future occurrence of NMSC. Patients treated with ALA-PDT require thorough education to ensure that they adhere to all treatment recommendations and are prepared to manage local reactions. Additionally, regardless of whether patients receive treatment with ALA-PDT, all patients with AK should be educated regarding signs and symptoms that may indicate progression to NMSC and require further evaluation.

DISCLOSURES

JG is a consultant, advisor, and/or speaker for AbbVie, Inc.; Beiersdorf; Celgene Corporation; Dermira; Eli Lilly and Company; Encore Dermatology, Inc.; Foamix Pharmaceuticals Ltd; LEO Pharma; Mayne Pharma; Novartis Pharmaceuticals; Ortho Dermatologics, Inc.; Primus Pharmaceuticals; PruGen Pharmaceuticals; Regeneron Pharmaceuticals, Inc.; Sanofi-Genzyme; Sun Pharmaceutical Industries, Inc.; and UCB S.A. SF is a consultant, advisor, and/or speaker for AbbVie, Inc.; Eli Lilly and Company; Novartis, and UCB.

ACKNOWLEDGMENT

Medical writing and editorial support was provided by Judith M. Phillips, DVM, PhD, CMPP, of AlphaBioCom, LLC, and funded by Sun Pharmaceutical Industries, Inc.

REFERENCES

1. Berman B, Bhatia N, Piacquadio D, et al. Efficacy of aminolevulinic acid 20 % solution photodynamic therapy in the treatment of actinic keratoses on the upper extremities: A post hoc analysis of a phase 3, randomized, vehicle-controlled trial. *Photodiagnosis Photodyn Ther.* 2020;32:102013.
2. Cerio R, Dirschka T, Dreno B, et al. Actinic keratosis, a chronic, progressive disease: Understanding clinical gaps to optimise patient management. *Acta Derm Venereol.* 2017;97(8):997-998.
3. de Berker D, McGregor JM, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol.* 2017;176(1):20-43.
4. Del Rosso JQ, Kircik L, Goldenberg G, Brian B. Comprehensive management of actinic keratoses: practical integration of available therapies with a review of a newer treatment approach. *J Clin Aesthet Dermatol.* 2014;7(9 Suppl S2-S12):S2-S12.
5. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer.* 2009;115(11):2523-2530.
6. Sachdeva S. Fitzpatrick skin typing: applications in dermatology. *Indian J Dermatol Venereol Leprol.* 2009;75(1):93-96.
7. Poulin Y, Lynde CW, Barber K, et al. Non-melanoma skin cancer in Canada chapter 3: Management of actinic keratoses. *J Cutan Med Surg.* 2015;19(3):227-238.
8. Peris K, Calzavara-Pinton PG, Neri L, et al. Italian expert consensus for the management of actinic keratosis in immunocompetent patients. *J Eur Acad Dermatol Venereol.* 2016;30(7):1077-1084.
9. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. *J Eur Acad Dermatol Venereol.* 2015;29(11):2069-2079.
10. Hofbauer G, Anliker M, Boehncke WH, et al. Swiss clinical practice guidelines on field cancerization of the skin. *Swiss Med Wkly.* 2014;144:w14026.
11. Richard MA, Amici JM, Basset-Seguin N, et al. Management of actinic keratosis at specific body sites in patients at high risk of carcinoma lesions: expert consensus from the AKTeam of expert clinicians. *J Eur Acad Dermatol Venereol.* 2018;32(3):339-346.
12. PharmaLetter T. Denmark's LEO Pharma initiates Picato phase-out. 2020; https://www.thepharmaletter.com/article/denmark-s-leo-pharma-initiates-picato-phase-out. Accessed March 10, 2021.
13. Fleming P, Zhou S, Bobotsis R, Lynde C. Comparison of the treatment guidelines for actinic keratosis: A critical appraisal and review. *J Cutan Med Surg.* 2017;21(5):408-417.
14. Almirall. Almirall announces FDA approval of Klisyri® (tirbanibulin), a new innovative topical treatment for actinic keratosis. 2020; https://www.almirall.com/newsroom/news/almirall-announces-fda-approval-of-klisyri%C2%AE-tirbanibulin-a-new-innovative-topical-treatment-for-actinic-keratosis. Accessed March 10, 2021.
15. Brian Jiang SI, Kempers S, Rich P, et al. A randomized, vehicle-controlled phase 3 study of aminolevulinic acid photodynamic therapy for the treatment of actinic keratoses on the upper extremities. *Dermatol Surg.* 2019;45(7):890-897.
16. Ozog DM, Rkein AM, Fabi SG, et al. Photodynamic therapy: A clinical consensus guide. *Dermatol Surg.* 2016;42(7):804-827.
17. Borgia F, Giuffrida R, Caradonna E, et al. Early and late onset side effects of photodynamic therapy. *Biomedicines.* 2018;6(1).
18. Levulan Kerastick [product label]. Sun Dermatology W, MA. March 2018.
19. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol. 2004;140(1):41-46.
20. Tschen EH, Wong DS, Pariser DM, et al. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol.* 2006;155(6):1262-1269.
21. Piacquadio D, Houlihan A, Ferdon MB, et al. A randomized trial of broad area ALA-PDT for field cancerization mitigation in high-risk patients. *J Drugs Dermatol.* 2020;19(5):452-458.

AUTHOR CORRESPONDENCE

Joe Gorelick MSN FNP-C
E-mail:..... jgorelick1@me.com

DERMATOLOGY AUTHORITY

THE PREMIER RESOURCE FOR DERMATOLOGY PRACTICES AND JOB SEEKERS

WHO WE ARE

Over the course of my career in working with thousands of dermatology practices, dermatologists and residency programs, I found that there was an overwhelming demand to bring practices and new providers together as well as help practices obtain the tools to thrive in an ever changing healthcare market.

That's how Dermatology Authority came to be: It emerged as a response to these and other requests that this unique community of dermatologists inquired.

Our mission; For dermatologists to stay focused on patient care, let our trusted advisors help you grow your practice.

- KIM CAMPBELL
FOUNDER AND
CHIEF ADVISOR

WHAT WE DO

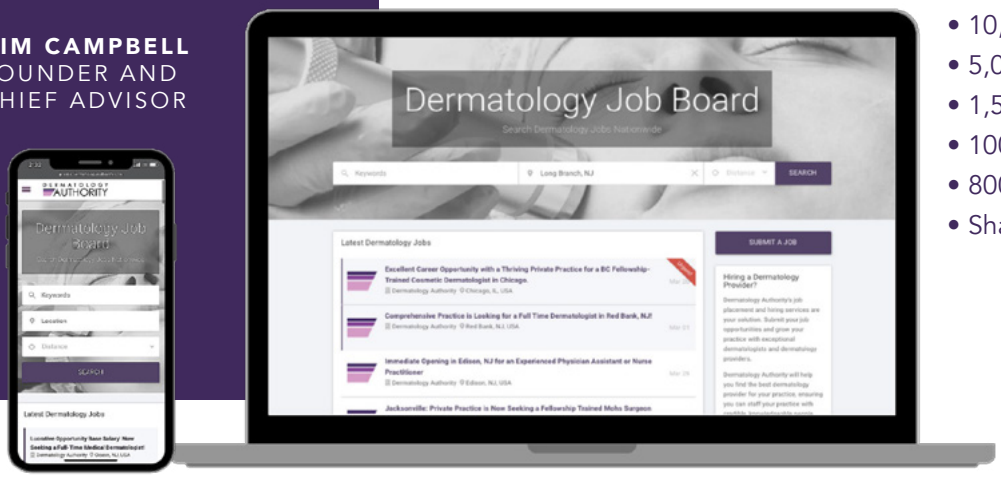
Dermatology Authority matches Dermatologists with practices based on what each party is looking for. We help practices find the best dermatology providers, ensuring practice growth with credible and complementary associates. Our hiring and job placement consultation services have successfully partnered many Dermatoogists saving time and resources.

You tell us what you are looking for and we will find it!

RECRUITING SERVICES

- **PROFESSIONAL GOALS**
- **CAREER ADVISEMENT**
- **GEOGRAPHIC LOCATION ANALYSIS**
- **PRACTICE START-UP**
- **MARKET STATS**
- **INTERVIEW GUIDANCE**
- **CONTRACT NEGOTIATION**
- **INDUSTRY REFERRALS**

POST ON OUR JOB BOARD



- 10,000+ monthly page views
- 5,000+ active users
- 1,500+ active candidates
- 100+ new monthly applicants
- 800+ job alert subscribers
- Share on our social media platforms

DERMATOLOGYAUTHORITY.COM
INFO@DERMATOLOGYAUTHORITY.COM • 1-800-577-0125

doi:10.36849/JDD.6040

November 2021 1246 Volume 20 • Issue 11

Copyright © 2021

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

An Overview of Biologics for Psoriasis

Rachna Dave MD, Amena Alkeswani MD

University of Tennessee Health Science Center, Memphis, TN

INTRODUCTION

The use of biologics has revolutionized the treatment of psoriasis but choosing the right agent could be challenging. Currently, there are multiple biologic options, each with advantages and disadvantages. This table is an overview of the relevant pharmacological properties, efficacy data, and considerations pertaining to patients' comorbidities to take into account when selecting a biologic.

TABLE

	MOA[1]	Route[1]	Dose + Frequency[1]	FDA-Approved Indications[1]	Time to See Response[1]	Pros in Psoriasis[1]	Pros Overall	Cons[1]	Comorbidities in Which to Use[1-3]	Comorbidities in Which to Avoid[1-3]	PASI 75 SCORE [1]
Etanercept (Enbrel)	TNF-α Inhibitor	SQ -Fixed dosing	50mg 2x/week for 12 weeks, then 50mg weekly	- PsO - PsA - AS - RA - JIA	12–16 weeks	- Approved for patients ≥ age 4yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Pustular PsO	- Anti-drug Abs not associated with loss of efficacy[1]	- Frequent SQ dosing - Slower onset of action compared to newer medications[4] - May worsen IBD[5]	- IBD+ (EXCEPTION: Etanercept) - CVD+ - HBV*, HCV** - HIV***	- MS (CI) - CHF Class III or IV (CI) - Concurrent or prior malignancy	At week 12: - 49% if 50mg twice per week - 33% if 50mg weekly
Adalimumab (Humira)	TNF-α Inhibitor	SQ -Fixed dosing	80mg at week 0, 40mg at week 1, then 40mg q2 weeks	- PsO (adults) - PsA - AS - RA - IBD - JIA - HS - Uveitis		- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO	- Approved for adult and pediatric Crohn's[1]	- Frequent SQ dosing - Loss of efficacy via anti-drug Abs			At week 16: - 71%
Infliximab (Remicade)	TNF-α Inhibitor	IV -Weight-based dosing	5mg/kg at weeks 0, 2, 6, then q8 weeks	- PsO - PsA - AS - RA - IBD	8–10 weeks	- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Palmoplantar pustular PsO - Generalized pustular PsO	- Approved for adult and pediatric IBD[1]	- IV administration - Loss of efficacy via anti-drug Abs (prevention= MTX) - Infusion reactions			At week 10: - 75.5% if dosed at 5mg/kg - 70.3% if dosed at 3mg/kg
Certolizumab (Cimzia)	Pegylated TNF-α Inhibitor	SQ -Fixed dosing	- 400mg (as 2 200mg injections) q2 weeks - If ≤90kg: 400mg (as 2 200mg injections) at weeks 0, 2, 4, then 200mg q2 weeks	- PsO - PsA - AS - RA - Crohn's	12–16 weeks	- May be used in pregnancy-minimal crossing of placental barrier[6,7]	- Increased T1/2	- Frequent SQ dosing			At week 12: - 75% if 200mg q2 weeks - 83% if 400mg q2 weeks
Ustekinumab (Stelara)	IL-12 and IL-23 Inhibitor	SQ -Weight-based dosing	- If ≤100kg: 45mg at weeks 0 and 4, then q12 weeks - If >100kg: 90mg at weeks 0 and 4, then q12 weeks - If age 12–17yrs and <60kg: 0.75mg/kg at 0 and 4, then q12 weeks	- PsO - PsA - Crohn's	12 weeks	- Approved for patients ≥ age 12yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Palmoplantar pustular PsO - Annular pustular PsO - Generalized pustular PsO	- q3mos dosing	- Less effective than TNF-α inhibitors for PsA - Loss of efficacy via anti-drug Abs	- IBD+ - Obesity+ - CHF+ - MS - HBV*, HCV** - HIV***		At week 12: - 66.7-67.1% if 45mg dose - 66.4-75.7% if 90mg dose
Guselkumab (Tremfya)	IL-23 Inhibitor	SQ	100mg at weeks 0 and 4, then q8 weeks	- PsO - PsA[8]	12 weeks	- Scalp + nail PsO - Palmoplantar PsO	- q2mos dosing - Neutralizing anti-drug Abs not associated with loss of efficacy or injection-site reactions[1]	- Slower onset of action + clinical improvement compared to IL-17 inhibitors[9]	- IBD - Obesity+ - CHF+ - HIV***		At week 16: - 86.3[10] - 91.2%[11]

TABLE (CONTINUED)

Tildrakizumab (Ilumya)	IL-23 Inhibitor	SQ	100mg at weeks 0 and 4, then q12 weeks	- PsO			- q3mos dosing	- Slower onset of action + clinical improvement compared to IL-17 inhibitors[9] - Loss of efficacy via neutralizing anti-drug Abs			At week 12: - 61% if 100mg dose - 66% if 200mg dose
Risankizumab (Skyrizi)	IL-23 Inhibitor	SQ	150mg at weeks 0 and 4, then q12 weeks	- PsO[12]			- q3mos dosing	- Slower onset of action/clinical improvement compared to IL-17 inhibitors[9]			At week 12: - 63% if 18mg dose - 98% if 90mg dose - 88% if 180mg dose[13]
Secukinumab (Cosentyx)	IL-17A Inhibitor	SQ	300mg weekly at weeks 0–4, then q4 weeks	- PsO (adults) - PsA - AS - Non-radiographic axial spondylo-arthritis[14]	12 weeks	- Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO - Neck PsO	- Rapid onset of action[4] - Maintenance of response at 52 weeks of q4 week dosing - Neutralizing anti-drug Abs not associated with loss of efficacy[1]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections	- Obesity* - CHF* - MS - HBV*, HCV** - HIV***	IBD (May worsen)	At week 12: - 71.6-77.1% if 150mg dose - 77.1-81.6% if 300mg dose
Ixekizumab (Taltz)	IL-17A Inhibitor	SQ	- Initial: 160mg at week 0, then 80mg q2 weeks from weeks 2–12 - Maintenance: 80mg q4 weeks - Some may require 80mg q2 weeks	- PsO - PsA - AS - Non-radiographic axial spondylo-arthritis[16]		- Approved for patients ≥ age 6yrs - Scalp + nail PsO - Erythrodermic PsO - Palmoplantar PsO - Generalized pustular PsO - Inverse PsO - Genital PsO	- Rapid onset of action[4]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections - Loss of efficacy via neutralizing anti-drug Abs			At week 12: - 84.2%
Brodalumab (Siliq)	IL-17RA Antagonist	SQ	- Initial: 210mg weekly at weeks 0–2 - Maintenance: 210mg q2 weeks	- PsO		- Scalp + nail PsO - Erythrodermic PsO - Generalized pustular PsO	- Rapid onset of action[4] - No neutralizing anti-drug Abs[1]	- May worsen IBD[15] - Increased infection risk - Risk of mucocutaneous Candida infections - BBW: suicidal ideation and behavior[17]			At week 12: - 67-69% if 140mg dose - 85-86% if 210mg dose

*Preferred
†If active HBV infection (HBsAg+), may require concurrent antiviral treatment and specialist evaluation. If cleared infection (anti-HBc+), no need for close follow-up; will only require regular monitoring for reactivation with HBsAg, anti-HBc, and liver enzymes.
**With management of active infection by health care provider.
***Use with caution. Only initiate if patient is receiving HAART, has a normalized CD4+ T cell count, no detectable viral load, and no history of opportunistic infection. Consult the patient's infectious disease provider prior to initiation.

Abbreviations: Tumor necrosis factor (TNF), Subcutaneous (SQ), Psoriasis (PsO), Psoriatic arthritis (PsA), Ankylosing spondylitis (AS), Rheumatoid arthritis (RA), Juvenile idiopathic arthritis (JIA), Inflammatory bowel disease (IBD), CVD (cardiovascular disease), Hepatitis B (HBV), Hepatitis C (HCV), Human immunodeficiency virus (HIV), Multiple sclerosis (MS), Congestive heart failure (CHF), CI (contraindicated), Hidradenitis suppurativa (HS), Antibodies (Abs), Intravenous (IV), Methotrexate (MTX), Interleukin (IL), Black Box warning (BBW).

DISCUSSION

The authors have disclosed no conflicts.

REFERENCES

1. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-1072.
2. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019;80(1):27-40.
3. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Focus on special populations and chronic infections. J Am Acad Dermatol. 2019;80(1):43-53.
4. Papp KA, Lebwohl MG. Onset of action of biologics in patients with moderate-to-severe psoriasis. J Drugs Dermatol. 2017;17(3):247-250.
5. Nehring P, Przybylkowski A. Is psoriasis treatment a risk factor for inflammatory bowel disease? Pharmaceut Med. 2020;34(4):257-262.
6. Lebwohl M, Blauvelt A, Paul C, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). J Am Acad Dermatol. 2018;79(2):266-276 e265.
7. Mariette X, Forger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018;77(2):228-233.
8. Tremfya. Package Insert. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761061s007lbl.pdf. Cited on: 10/30/2020.
9. Warren RB, Gooderham M, Burge R, et al. Comparison of cumulative clinical benefits of biologics for the treatment of psoriasis over 16 weeks: Results from a network meta-analysis. J Am Acad Dermatol. 2020;82(5):1138-1149.
10. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76(3):418-431.
11. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-417.
12. Skyrizi. Package Insert. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761105s000lbl.pdf. Cited on: 10/30/2020.
13. Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2017;376(16):1551-1560.
14. Cosentyx. Package Insert. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125504s035lbl.pdf Cited on 10/30/2020.
15. Reich K, Leonardi C, Langley RG, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. J Am Acad Dermatol. 2017;76(3):441-448 e442.
16. Taltz. Package Insert. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125521s016lbl.pdf Cited on 10/30/2020.
17. Siliq. Package Insert. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf. Cited on: 10/30/2020.

AUTHOR CORRESPONDENCE

Amena Alkeswani MD
E-mail:..... aalkeswa@uthsc.edu

doi:10.36849/JDD.6088

November 2021 1248 Volume 20 • Issue 11

Copyright © 2021

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Examining Trends in Dermatology Publications: A 10-Year Follow-up

Reem Qabas Al Shabeeb MD,[a,b] Kamaria Nelson MD,[c] Kelley Pagliai Redbord MD[d]

[a]School of Medicine and Health Sciences, The George Washington University, Washington, DC,
[b]Department of Internal Medicine, Inova Fairfax Medical Campus, Falls Church, VA
[c]Department of Dermatology, School of Medicine and Health Sciences, The George Washington University, Washington, DC
[d]Dermatology and Dermatologic Surgery Group of Northern Virginia, Vienna, VA

ABSTRACT

Introduction: Examining trends in adult and pediatric dermatology publications by Mimouni et al for 15 years (1993–2007) showed that there was a higher yearly increase in articles with higher level of evidence such as clinical and randomized controlled trials with a slower rise in articles with a lower level of evidence such as letters and case reports.[1] We wanted to see if trends in dermatology research have differed over the following 10 years (2008–2017).

Methods: We used the methodology of Mimouni et al to find the total number and categorization of publications in adult and pediatric dermatology from 2008 to 2017. We used MEDLINE to search the terms 'skin' AND 'disease' OR 'dermatology' for adults and pediatrics. A regression analysis (SAS 9.4) was used to understand the change in frequency across the years.

Results and Discussion: By analyzing publications from 2008 to 2017, speculations mentioned in Mimouni et al held true regarding the statistically significant increase in total number of publications in addition to meta-analyses and practice guidelines, which was not shown in the 1993–2007 analysis. The statistically significant increase previously mentioned in clinical trials, case reports, and pediatric randomized controlled trials was lost in the 2008-2017 data.

Conclusion: Trends in pediatric and adult dermatology publications in 2008–2017 differ from those identified in 1993–2007. There is a new significant increase in higher level of evidence not reported previously such as meta-analyses and practice guidelines. This is good for dermatology, and we hope the trend continues to further the specialty.

J Drugs Dermatol. 2021;20(11)1248-1251. doi:10.36849/JDD.6088

INTRODUCTION

According to Mimouni et al, dermatology publication trends from 1993 to 2007 revealed a faster increase in high level of evidence studies such as clinical and randomized controlled trials, and a slower rise in articles providing low level of evidence such as case reports and letters.[1,2] Mimouni et al speculated that the expansion of electronic resources and the internet revolution may create changes different than the trends reported.[1] They also speculated that the rise in clinical and randomized controlled trials reported in their study would lead to a rise in meta-analyses in the upcoming years.[1] We sought to evaluate if dermatology publication trends identified in 1993–2007 holds true for the next decade or if there are any changes. Examining these trends will aid dermatologists in understanding the evidence level of new publications and guiding researchers in areas where our field lacks.

MATERIALS AND METHODS

We followed the methodology of Mimouni et al to find the total number and categorization of publications in adult and pediatric dermatology. MEDLINE is a free service provided by the US National Library of Medicine that is commonly used in academia to find medical literature.[3] A MEDLINE search, http:www.ncbi.nlm.nih.gov/, of the keywords 'skin' AND 'disease' OR 'dermatology' from 1 January 2008 to 31 December 2017 was performed. Adult publications were determined by selecting 'all adults' (19 years and above) while pediatric publications were determined by selecting 'all child' (0–18 years). The search category was limited to 'humans' and to articles written in English. We also utilized MEDLINE's classification of articles into different categories such as clinical trials, editorials, letters, meta-analysis, practice guidelines, randomized controlled trials, reviews, case reports, and systematic reviews. A simple regression analysis using SAS version 9.4 (SAS Institute Inc., Cary, NC) was performed to analyze trends. A p-value of ≤0.05 was considered significant and a p-value of ≤0.10 was considered marginally significant.

RESULTS

From the years 2008 to 2017 there were 72,765 adult publications and 29,831 pediatric. Raw results obtained from MEDLINE for adult and pediatric dermatology publications along with the categorization are depicted in Tables 1 and 2.

TABLE 1.

Raw Data for Publications in Adult Dermatology from 2008–2017. Percentages (%) are in parentheses.

Year	Total	Clinical Trials	Editorials	Letters	Meta-Analyses	Practice Guidelines	Randomized Controlled Trials	Reviews	Case Reports	Systematic Reviews
2008	5605	580 (10.3)	2 (0.0)	311 (5.5)	4 (0.1)	3 (0.1)	346 (6.2)	315 (5.6)	2461 (43.9)	45 (0.8)
2009	5809	594 (10.2)	6 (0.1)	320 (5.5)	6 (0.1)	3 (0.1)	371 (6.4)	327 (5.6)	2349 (40.4)	50 (0.9)
2010	5882	639 (10.9)	8 (0.1)	253 (4.3)	9 (0.2)	4 (0.1)	385 (6.5)	339 (5.8)	2280 (38.8)	52 (0.9)
2011	6340	668 (10.5)	2 (0.0)	270 (4.3)	17 (0.3)	8 (0.1)	385 (6.1)	362 (5.7)	2272 (35.8)	74 (1.2)
2012	6697	759 (11.3)	3 (0.0)	307 (4.6)	25 (0.4)	4 (0.1)	447 (6.7)	372 (5.6)	2353 (35.1)	79 (1.2)
2013	7699	780 (10.1)	3 (0.0)	791 (10.3)	27 (0.4)	3 (0.0)	483 (6.3)	408 (5.3)	2893 (37.6)	101 (1.3)
2014	8957	811 (9.1)	5 (0.1)	1438 (16.1)	17 (0.2)	4 (0.0)	520 (5.8)	453 (5.1)	3562 (39.8)	89 (1.0)
2015	9750	892 (9.1)	7 (0.1)	1504 (15.4)	46 (0.5)	2 (0.0)	605 (6.2)	531 (5.4)	3690 (37.8)	121 (1.2)
2016	9620	803 (8.3)	11 (0.1)	1329 (13.8)	53 (0.6)	5 (0.1)	551 (5.7)	481 (5.0)	3408 (35.4)	156 (1.6)
2017	6406	567 (8.9)	4 (0.1)	384 (6.0)	43 (0.7)	4 (0.1)	394 (6.2)	379 (5.9)	1958 (30.6)	144 (2.2)

TABLE 2.

Raw Data for Publications in Pediatric Dermatology from 2008–2017. Percentages (%) are in parentheses.

Year	Total	Clinical Trials	Editorials	Letters	Meta-Analyses	Practice Guidelines	Randomized Controlled Trials	Reviews	Case Reports	Systematic Reviews
2008	2317	190 (8.2)	3 (0.1)	69 (3.0)	4 (0.2)	2 (0.1)	140 (6.0)	231 (10.0)	736 (31.8)	25 (1.1)
2009	2435	208 (8.5)	6 (0.2)	82 (3.4)	4 (0.2)	5 (0.2)	158 (6.5)	204 (8.4)	749 (30.8)	36 (1.5)
2010	2631	220 (8.4)	15 (0.6)	68 (2.6)	8 (0.3)	4 (0.2)	154 (5.9)	240 (9.1)	822 (31.2)	35 (1.3)
2011	2744	231 (8.4)	2 (0.1)	69 (2.5)	12 (0.4)	6 (0.2)	145 (5.3)	242 (8.8)	813 (29.6)	42 (1.5)
2012	2868	251 (8.8)	6 (0.2)	74 (2.6)	14 (0.5)	1 (0)	173 (6.0)	237 (8.3)	891 (31.1)	43 (1.5)
2013	3199	248 (7.8)	5 (0.2)	181 (5.7)	12 (0.4)	6 (0.2)	173 (5.4)	305 (9.5)	1009 (31.5)	62 (1.9)
2014	3610	260 (7.2)	9 (0.2)	369 (10.2)	11 (0.3)	4 (0.1)	185 (5.1)	294 (8.1)	1156 (32.0)	54 (1.5)
2015	3760	263 (7.0)	4 (0.1)	398 (10.6)	25 (0.7)	9 (0.2)	203 (5.4)	321 (8.5)	1157 (30.8)	79 (2.1)
2016	3678	242 (6.6)	5 (0.1)	356 (9.7)	34 (0.9)	9 (0.2)	181 (4.9)	317 (8.6)	1004 (27.3)	112 (3.0)
2017	2589	190 (7.3)	2 (0.1)	109 (4.2)	14 (0.5)	13 (0.5)	145 (5.6)	217 (8.4)	620 (23.9)	85 (3.3)

TABLE 3.

Statistical Analysis for Publications in Adult Dermatology from 2008–2017.

Type of Study/Publication	r/rho/ρ	R^2	p-value
Total	0.7053	0.4975	0.0227*
Clinical Trials	0.4929	0.2429	0.1478
Editorials	0.3578	0.1280	0.3100
Letters	0.6218	0.3867	0.0549 #
Meta-Analyses	0.9121	0.8319	0.0002*
Practice Guidelines	0.0000	0.0000	1.0000
Randomized Controlled	0.6783	0.4600	0.0311*
Reviews	0.7549	0.5699	0.0116*
Case Reports	0.4241	0.1799	0.2219
Systematic Reviews	0.9587	0.9191	<.0001*

A statistically significant value of $P<0.05$ is denoted by an asterisk symbol (*) while a marginally significant value of $P<0.10$ is denoted by a dash (#) symbol.

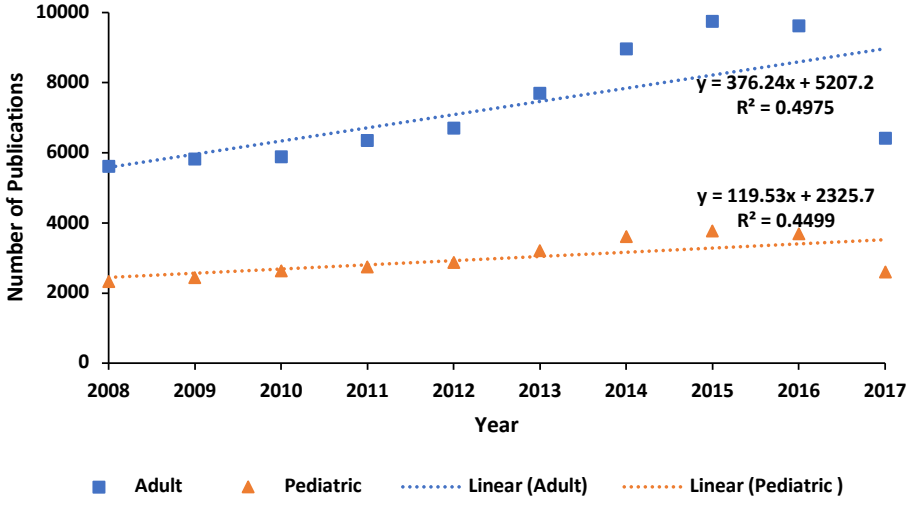
TABLE 4.

Statistical Analysis for Publications in Pediatric Dermatology from 2008–2017.

Type of Study/Publication	r/rho/ρ	R^2	p-value
Total	0.6708	0.4499	0.0337*
Clinical Trials	0.3616	0.1308	0.3045
Editorials	-0.2407	0.0579	0.5030
Letters	0.6453	0.4164	0.0439*
Meta-Analyses	0.7521	0.5656	0.0121*
Practice Guidelines	0.7688	0.5911	0.0094*
Randomized Controlled	0.5087	0.2588	0.1332
Reviews	0.5428	0.2946	0.1050
Case Reports	0.3606	0.1300	0.3061
Systematic Reviews	0.9062	0.8211	0.0003*

A statistically significant value of P<0.05 is denoted by an asterisk symbol (*).

FIGURE 1. Correlation between the total number of adult and pediatric dermatology publications from 2008–2017.



For adult dermatology publication trends (Table 3), there was a significant increase in total number of publications (R^2=0.4975, *P*=0.0227), meta-analyses (R^2=0.8319, *P*=0.0002), randomized controlled trials (R^2=0.4600, *P*=0.0311), reviews (R^2=0.5699, *P*=0.0116) and systematic reviews (R^2=0.9191, *P*<.0001). For pediatric dermatology publication trends (Table 4), there was a significant increase in total number of publications (R^2=0.4499, *P*=0.0337), letters (R^2=0.4164, *P*=0.0439), meta-analyses (R^2=5656, *P*=0.0121), practice guidelines (R^2=0.5911, *P*=0.0094) and systematic reviews (R^2=0.8211, *P*=0.0003). By analyzing frequencies, case reports continue to make up the largest percentage of published data in dermatology; by summing up all publications across the years, case reports make up 37.4% of adult publications and 30% of pediatric publications. Figure 1 shows the correlation between the total number of adult and pediatric dermatology publications.

DISCUSSION

Mimouni et al examined trends in adult and pediatric dermatology publications for 15 years (1993–2007) and found that there was an increase in total number of publications, randomized controlled trials, clinical trials, case reports, and letters to the editors across the years.[1] The regression analysis for meta-analyses, editorials, and practice guidelines in the original article was limited due to the low number of publications.[1] In comparing the quality of the published work, the fastest rate of increase reported in Mimouni et al was for publications with a higher level of evidence such as clinical trials and randomized controlled trials while articles with a lower level of evidence such as letters to the editors and case reports had a slower rate of increase or no change.[1]

Our analysis for the next 10 years (2008–2017) showed a similar significant increase for both adult and pediatric dermatology in the total number of publications. In adult dermatology, similar to what was found in Mimouni et al, there was a significant increase in randomized controlled trials. However, new trends include a significant increase in reviews, systematic reviews, and meta-analysis. In pediatric dermatology, new trends include the statistically significant increase in meta-analyses, practice guidelines, and systematic reviews. The statistically significant increase previously observed in 1993–2007 in clinical trials, case reports, and pediatric randomized controlled trials was lost in the 2008–2017 data. As was observed in Mimouni et al, case reports continued to make up the largest percentage of publications in 2008–2017. This may be attributed to the relatively low number of FDA-approved treatments for dermatologic conditions, necessitating the need for case reports to discover off-label therapeutic options. Further, case reports are necessary in understanding new disease entities or novel treatments and can serve to stimulate further research thus, our results confirm the utility of case reports in dermatology.

The field of dermatology has expanded for the last 25 years. Examining trends in adult and pediatric publications can help dermatologists understand the current state of research in the field. It can also aid in pointing researchers to areas that need further investigation and development, like pediatric randomized controlled trials. The increase in meta-analyses and practice guidelines is promising and we hope it continues to empower the field of dermatology.

Some limitations in this study include ones originally mentioned in Mimouni et al regarding the overlap between pediatric and adult publications that can't be differentiated in MEDLINE, the default categorization of MEDLINE that may not be accurate, and the inability of MEDLINE to include absolutely all articles in dermatology. As discussed in Mimouni et al, we do not

expect that these differences could have significantly impacted our analysis. The limited use of the keywords was a limitation mentioned in Mimouni et al that we did not work on expanding as we wanted to maintain our ability to compare our results to theirs. Finally, as MEDLINE is dynamic with articles being added periodically, we cannot compare the exact numbers in our study to that of Mimouni et al as the numbers would have differed by now; for example, at the time the study by Mimouni et al was analyzed, there were 910 adult publications with 26 randomized controlled trials in the search year 1993. Repeating the search criteria in June of 2018 for the year 1993 resulted in 2605 adult publications with 117 randomized controlled trials. The corresponding author of Mimouni et al was contacted to confirm our use of the correct search criteria as outlined in the methods section of the paper.

CONCLUSIONS

By analyzing the trends in adult and pediatric dermatology publications from 2008–2017, new trends have been found compared to the 1993–2007 analysis. The new statistically significant increase in higher level of evidence publications such as meta-analyses and practice guidelines is encouraging to the current state of research in the field of dermatology.

ACKNOWLEDGEMENTS

We thank Andrew D. Sparks who completed the statistical analysis for this work.

DISCLOSURES

All authors declare no conflict of interest.

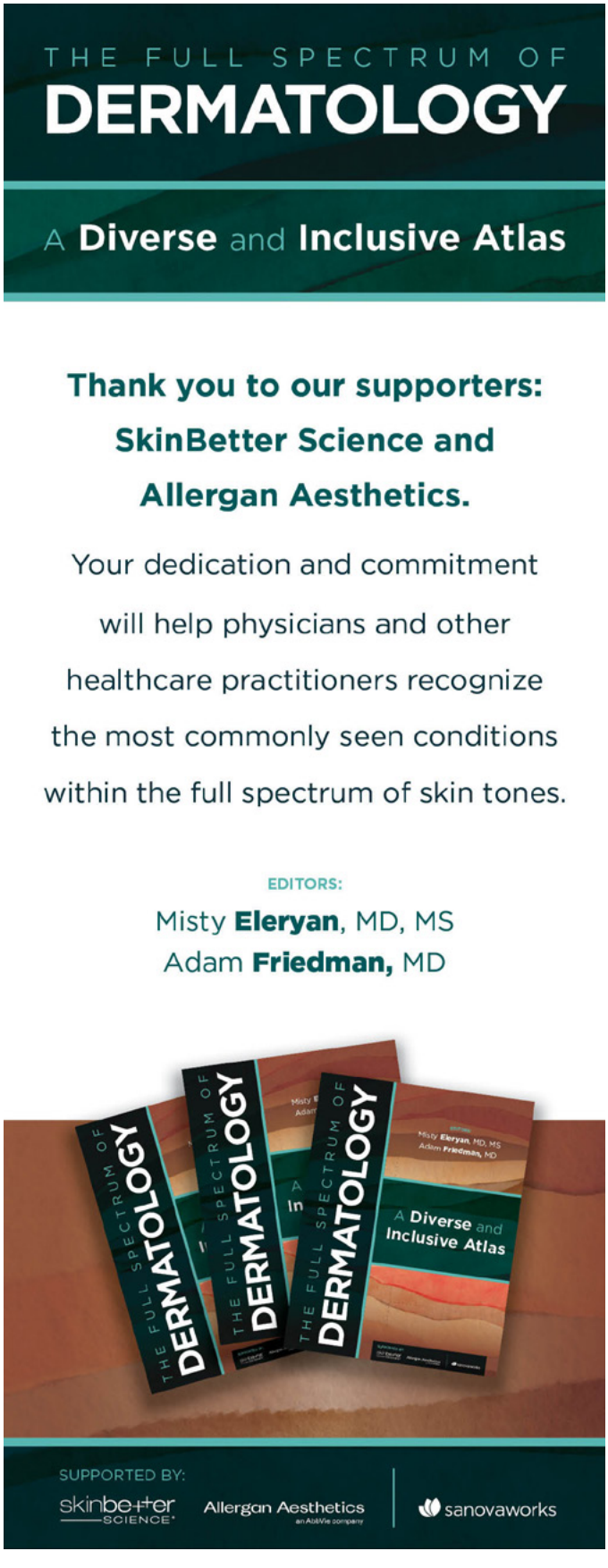
REFERENCES

1. Mimouni D, Pavlovsky L, Akerman L, David M, Mimouni FB. Trends in dermatology publications over the past 15 years. *Am J Clin Dermatol.* 2010;11(1):55-58. doi:10.2165/11530190-000000000-00000
2. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA.* 1992;268(17):2420-2425. doi:10.1001/jama.1992.03490170092032
3. Shashikiran ND. MEDLINE, PubMed, and PubMed central (®): Analogous or dissimilar. *J Indian Soc Pedod Prev Dent.* 2016;34(3):197-198. doi:10.4103/0970-4388.186748

AUTHOR CORRESPONDENCE

Reem Al Shabeeb MD

E-mail:..... reem_shabeeb@gwmail.gwu.edu



doi:10.36849/JDD.6174

November 2021 1252 Volume 20 • Issue 11

Copyright © 2021

Journal of Drugs in Dermatology

Patients Frequently Overestimate Their Comprehension of Common Mohs Micrographic Surgery Terms: A Cross-Sectional Survey

Peter Chow MD,[a] Brett C. Neill MD,[b] Edward W. Seger MD MS,[a] Spyros M. Siscos MD,[a] Jace J. Rickstrew MD,[a] Ian Graham BS,[b] Anand Rajpara MD,[a] Thomas L.H. Hocker MD[a]

[a]Division of Dermatology, University of Kansas Medical Center, Kansas City, KS
[b]University of Kansas School of Medicine, Kansas City, KS

ABSTRACT

Background: Patients who understand their diagnosis and treatment are more likely to be satisfied with their care and more compliant with treatment. Dermatologic surgery is a specialized field with associated jargon that many patients may not understand.
Objective: The aim of the study was to assess patient understanding of dermatology medical terminology.
Methods: This was a single-blinded study conducted with patients 18 years and older from an academic dermatology clinic surveying patients on 12 terms that are frequently used in dermatologic surgery. Participants rated their level of confidence in their understanding of each term using a 5-point Likert scale, followed by explaining the definition of the term. 3 blinded physicians graded each participant's definition using a 5-point scale of accuracy of understanding, designed to mimic the Likert scale.
Results: A total of 200 respondents completed the survey (96% response rate). The average term perceived understanding was 3.90 ±0.66, the average term accuracy was 3.26±0.93. Patients overestimated their understanding 44% of the time, and underestimated their knowledge 17% of the time. The terms with the lowest respondent confidence were the terms *secondary intention, Mohs surgery*, and *flaps*. The terms with the lowest respondent accuracy was *secondary intention, defect*, and *Mohs surgery*.
Conclusion: There is a gap in knowledge in commonly used dermatologic surgery terms among patients. Certain demographics appear to be more at risk for not understanding medical jargon or overestimating their understanding of terms. Obtaining these patient demographics may help to identify patients needing additional education regarding dermatologic surgery.

J Drugs Dermatol. 2021;20(11):1252-1254. doi:10.36849/JDD.6174

INTRODUCTION

Patient satisfaction and outcomes are impacted by an inability to understand medical jargon.[1,2] Further, patients often don't understand, or overestimate their understanding of dermatology terminology.[3-5] Comprehension during Mohs surgery is important as patients are alert during the procedure and uncertainty may increase anxiety levels. Moreover, lack of comprehension may impact adherence to post-operative recommendations and worsen clinical outcomes.

METHODS

An institutional review board-approved survey was conducted to assess patient comprehension of commonly used terms during Mohs surgery. Patients 18 and older were recruited from an academic dermatology clinic to complete a brief in-person survey which assessed comprehension of 12-terms. Each term was presented in a sentence for context. Participants rated their level of confidence in understanding each term using a 5-point Likert scale and then defined the term (5 denoted as extremely confident). Three blinded physicians graded each definition using a 5-point scale (termed "accuracy", 5 denoted as completely accurate). Student t-tests were used to identify associations between patient confidence and physician-graded accuracy of understanding ($P<0.05$ considered statistically significant). Fisher exact tests were substituted when parametric assumptions could not be verified.

RESULTS

Two-hundred respondents completed the survey (96% response rate) with an average age of 57 ± 20 years. Sixty percent were male, 90% white (3.5% black, 3% Asian, 2% Hispanic, 1.5% other) and 62% had a college degree (Table 1). The average patient confidence in Mohs terms was 3.90 ± 0.66, the average term accuracy was 3.26±0.93. Patients overestimated their knowledge (reported a confidence score higher than the physician graded accuracy score) 44% of the time. The terms patients were least confident in included *secondary intention and Mohs surgery*. The terms they were least accurate with included *secondary intention and defect* (table 2).

College educated patients were more confident (3.98 ± 0.70 vs 3.76 ± 0.70, $P<0.001$) and accurate (3.34 ± 0.98 vs 3.01 ± 0.91,

TABLE 1.

Demographic Comparison Between Confidence and Accuracy of Mohs Surgery Terms

	n	Overall score, mean (SD)		p-value	Underestimation (%)	p-value	Overestimation (%)	p-value
		Self	Physician					
Education								
High school	76	3.76 ± 0.7	3.01 ± 0.91	<0.0001[a] 0.0394[b]	16	0.3096[a] 0.0857[b]	47	0.04[a] 0.0774[b]
College	81	3.98 ± 0.70	3.34 ± 0.98		17		44	
Graduate School	43	3.99 ± 0.58	3.52 ± 0.94		20		39	
Age								
18-60	92	3.77 ± 0.67	3.17 ± 0.97	0.0184	19	0.0821	45	0.3864
61 and older	108	4.02 ± 0.66	3.33 ± 0.92		16		43	
Experience in medical field								
Yes	59	4.13 ± 0.55	3.48 ± 0.94	0.0002	16	<0.0001	44	0.5116
No	141	3.82 ± 0.71	3.18 ± 0.94		18		44	
Prior Mohs experience								
Yes	92	4.06 ± 0.62	3.58 ± 0.89	<0.0002	18	0.2775	39	<0.0001
No	108	3.77 ± 0.76	2.98 ± 0.99		16		49	
Family Medical Experience								
Yes	71	3.93 ± 0.63	3.23 ± 0.92	0.2831	16	0.0631	47	0.1557
No	129	3.90 ± 0.67	3.28 ± 0.95		16		43	

"Underestimation" is defined as instances when a patient reported a confidence lower than physician graded accuracy. "Overestimation" is defined as instanced when a patient reported a confidence higher than physician graded accuracy
Statistically significant values (p<0.05) denoted in bold
SD, Standard deviation
[a]p value comparison of high school vs college (including graduate school) education
[b]p value comparison of graduate school vs non-graduate school education

TABLE 2.

Term Specific Confidence and Accuracy

	Overall Score, mean (SD)				
Terms	Self	Physician	Underestimation %	Overestimation %	Common Accurate Definitions[a]
Suture	4.60 ± 0.88	4.47 ± 1.22	15	16	"Stitch"
Local Anesthetic	4.69 ± 0.71	4.14 ± 1.20	11	36	"Numbing"
Repair	4.24 ± 1.0	3.99 ± 1.29	30	35	"Closure"
Graft	4.37 ± 1.03	4.16 ± 1.28	24	28	"Piece of skin taken from one site to the other"
Margins	3.68 ± 1.37	3.24 ± 1.68	26	41	"Edge"
Defect	4.14 ± 1.09	2.19 ± 1.16	7	82	"Wound"
Layer	4.2 ± 1.12	3.35 ± 1.28	14	60	"A deeper or wider portion"
Flap	3.63 ± 1.36	3.03 ± 1.49	24	53	"Using nearby skin to cover wound"
Stages	4.17 ± 1.11	2.80 ± 1.27	10	69	"Another portion/part"
Excise	3.77 ± 1.44	3.96 ± 1.66	31	19	"Cut out" or "Remove"
Secondary Intention	2.51 ± 1.42	1.49 ± 1.20	9	55	"Heal on its own"
Mohs Surgery	2.89 ± 1.72	2.3 ± 1.57	9	39	"Tissue sparing surgery" or "Surgery for skin cancers in high risk or cosmetically sensitive areas"

SD, Standard deviation
[a]The most frequent accurate definitions patients gave that received full credit with physician grading.

P<0.0001) in their definitions compared to those without college degrees. Patients without college education also overestimated more frequently (47% vs 44% with a college degree, *P*=0.04). Patients over 60 were more confident (4.02 ± 0.66 vs 3.77 ± 0.67, *P*<0.0001) and accurate (3.33 ± 0.92 vs 3.17 ± 0.97, *P*=0.0184) when compared to younger patients. Patients with previous medical experience were more confident (4.13 ± 0.55 vs 3.82 ± 0.71, *P*<0.0001) and more accurate (3.48 ±0.94 vs 3.18 ± 0.94, *P*<0.001) compared to those without. Patients who previously underwent Mohs surgery were more confident (4.06 ± 0.62 vs 3.77 ± 0.76, *P*<0.0001), accurate (3.58 ± 0.89 vs 2.98 ± 0.99, *P*<0.0001), and less likely to overestimate (39% of the time vs 49%, *P*<0.0001) compared to those who had not.

DISCUSSION

This study is limited in diversity as a single institution sample; however, it illustrates the frequent lack of comprehension with Mohs surgery terms. Patients overestimated their knowledge nearly half of the time which reinforces the need to discuss with patients in non-medical terms to prevent instances of miscommunication and uncertainty.[4,5] We suggest using alternate terms or descriptive phrases patients are more familiar with, as demonstrated in table 2 under "Common Accurate Definitions." Further research can evaluate patient satisfaction and surgical complication rates when using simplified terminology.

DISCLOSURES

All authors listed above have no conflict of interest.

REFERENCES

1. Kutner, M, Greenberg E. and Baer J. (2006). A first look at the literacy of Americas adults in the 21st century. NCES 2006-470. Washington, DC: National Center for Education Statistics.
2. Graham S, Brookey J. Do patients understand? *Perm J.* 2008 Summer;12(3):67-9. doi: 10.7812/tpp/07-144. PMID: 21331214; PMCID:
3. Neill BC, Golda N, Seger EW, Wick J, Whitsitt J, Huber A, Chu T, Potts GA, Chow P, Moore S, Fakhoury JW, Rajpara A, Hocker TLH. Determining patient understanding of commonly used dermatology terms: A multicenter cross-sectional survey. *J Am Acad Dermatol.* 2020 Sep;83(3):933-935
4. Neill BC, Seger EW, Rickstrew JJ, Rajpara A. Reply to: "Missing the mark on patient comprehension". *J Am Acad Dermatol.* 2021;84(2):e117-e118. doi:10.1016/j.jaad.2020.10.022
5. Kelly PA, Haidet P. Physician overestimation of patient literacy: a potential source of health care disparities. *Patient Educ Couns.* 2007;66(1):119-122. doi:10.1016/j.pec.2006.10.007

AUTHOR CORRESPONDENCE

Brett C. Neill MD
E-mail:..... bcneill6@gmail.com

doi:10.36849/JDD.6098

November 2021 1255 Volume 20 • Issue 11

Copyright © 2021

Journal of Drugs in Dermatology

Successful Treatment of Palmoplantar Pustulosis With Apremilast

Noelle Dorgham MS-III, David Crasto DO, Stanley Skopit DO

Larkin Community Hospital Department of Dermatology, South Miami, FL

INTRODUCTION

Palmoplantar pustulosis (PPP) is a chronic, debilitating autoimmune skin disease characterized by the presence of recurrent neutrophilic pustules on acral surfaces. Although similarities exist, PPP is currently regarded as a distinct pathologic entity from palmoplantar psoriasis.[1] PPP is often refractory to topical treatments and therefore may benefit from the introduction of systemic or biologic therapy, although options are limited at this time. Few, yet promising, case reports exist highlighting the efficacy of oral apremilast, a phosphodiesterase-4 (PDE-4) inhibitor. Herein, we present a case of biopsy-proven PPP successfully treated with apremilast, along with a brief review of relevant literature supporting the use of apremilast.

CASE REPORT

A 39-year-old African American female with a 10 pack-year smoking history presented to the dermatology clinic with a 6-month history of pruritic skin lesions on her hands. Physical examination demonstrated crops of pustules with associated erythema and desquamation located on the palmar surface bilaterally (Figure 1); punch biopsy revealed subcorneal pustules with neutrophils and parakeratosis, consistent with a diagnosis of palmoplantar pustulosis.

FIGURE 1. Crops of pustules with surrounding erythema and desquamation observed prior to initiation of apremilast.

She was initially treated with topical corticosteroids in the form of triamcinolone acetonide ointment, followed by halobetasol ointment, with little to no relief. The decision was ultimately made to initiate systemic therapy with apremilast. Near-complete resolution of the lesions was observed following 8 weeks of treatment (Figure 1), with significant improvement in associated pruritis and overall quality of life according to the patient. Disease remission was maintained after 6 months, and the medication was well-tolerated by the patient without any reported side effects.

FIGURE 2. Remarkable improvement of lesions illustrated at 8 weeks of treatment with apremilast.

DISCUSSION

Apremilast works via PDE-4 inhibition, resulting in an upregulation of intracellular cyclic adenosine monophosphate (cAMP) and subsequent suppression of interleukin-2 (IL-2), interleukin-8 (IL-8), interferon gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α).[2,3] Furthermore, increased levels of IL-8 have been demonstrated in lesions of PPP. Given its neutrophil chemoattractant properties, IL-8 is implicated in the underlying development of PPP.[1] The efficacy of apremilast in PPP is therefore presumed to be an effect of IL-8 inhibition, thus preventing formation of the characteristic pustules.

PPP refractory to topical treatments may benefit from the introduction of systemic and/or biologic agents. Anecdotal reports of success with etanercept (TNF-α inhibition), ustekinumab (IL-12/23 inhibitions), and secukinumab (IL-17 inhibition) exist, however, evidence is lacking and inconclusive.[4-6] Guselkumab, an IL-23 inhibitor, has demonstrated efficacy in a randomized controlled trial (RCT) and is currently approved for PPP in Japan.[7]

Systemic agents including methotrexate, acitretin, and cyclosporine have all shown efficacy, however, the adverse side effects associated with the aforementioned agents makes their use disfavorable.[8] Side effects of apremilast, on the other hand, primarily consist of diarrhea and depression, which are typically

TABLE 1.

Case Studies Investigating The Use of Apremilast In Refractory Palmoplantar Pustulosis Have Been Promising Thus Far

Citation	Age, Gender	Apremilast Dose	Response	Adverse Events
Haebich, et al.[9]	75 years, female	30mg twice daily	Symptom resolution	None
Haller, et al.[10]	57 years, female	30mg twice daily	Significant improvement	None
Adamo, et al.[11]	24 years, female	30mg twice daily	Disease control	Headaches, diarrhea, nausea, vomiting, with spontaneous resolution
Mikhailitchenko, et al.[12]	53 years, male	30mg twice daily	Almost clear	Three patients experienced loose stools that did not warrant a change in dosing. One patient reported more severe symptoms, and the dose was halved to 30mg once daily.
Mikhailitchenko, et al.[12]	65 years, female	30mg twice daily	Clear	
Mikhailitchenko, et al.[12]	54 years, female	30mg once daily	Mild	
Mikhailitchenko, et al.[12]	66 years, female	30mg twice daily	Clear	
Mikhailitchenko, et al.[12]	63 years, female	30mg twice daily	Almost clear	
Mikhailitchenko, et al.[12]	43 years, male	30mg twice daily	Almost clear	
Mikhailitchenko, et al.[12]	39 years, female	30mg twice daily	Moderate	
Mikhailitchenko, et al.[12]	64 years, female	30mg twice daily	Almost clear	
Carrascosa de Lome, et al.[13]	77 years, female	30mg once daily	Near-complete resolution	Mild diarrhea with 30mg twice daily, reduced to 30mg once daily

mild and resolve upon discontinuation.[9] The low risk of internal toxicity and favorable side effect profile makes apremilast a safer and more viable option for systemic treatment of PPP compared to alternative systemic agents.

Previous reports have demonstrated similar efficacy of apremilast in the treatment of PPP (Table 1). In a single case study, a 75-year-old woman with an 8-year history of PPP reported symptomatic resolution within 4 weeks of therapy.[10] A similar study showing successful treatment with apremilast was also reported in a patient with rheumatoid arthritis who developed PPP after rituximab therapy.[11] Additionally, apremilast also proved efficacious in PPP associated with SAPHO syndrome.[7] Mikhailitcheneko et al. reported efficacy of apremilast in the treatment of PPP in a case series of 8 patients.[12] An additional case study recently provided further support for the use of apremilast in PPP.[13] Our case, along with previous reports, provides further evidence supporting the need for clinical trials in order to implement apremilast as an option for systemic therapy in patients with refractory PPP.

DISCLOSURES

The authors have reported no conflicts.

REFERENCES

1. Freitas E, Rodrigues MA, Torres T. Diagnosis, screening and treatment of patients with palmoplantar pustulosis (PPP): a review of current practices and recommendations. *Clin Cosmet Investig Dermatol.* 2020;13:561-578.
2. Bissonnette R, Pariser DM, Wasel NR, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. *J Am Acad Dermatol.* 2016;75(1):99-105.
3. Nassim D, Alajmi A, Jfri A, Pehr K. Apremilast in dermatology: A review of literature. *Dermatol Ther.* 2020 Sep 2:e14261.
4. Obeid G, Do G, Kirby L, Hughes C, Sbidian E, Le Cleach L. Interventions for chronic palmoplantar pustulosis. *Cochrane Database Syst Rev.* 2020 Jan;1(1):CD011628.
5. Bissonnette R, Poulin Y, Bolduc C, Maari C, Provost N, Syrotuik J, Poulin-Costello CM, Nigen S. Etanercept in the treatment of palmoplantar pustulosis. *J Drugs Dermatol.* 2008;7(10):940-946.
6. Hegazy S, Konstantinou MP, Livideanu CB, Tauber M, Uthurriague C, Paul C. Efficacy of ustekinumab in palmoplantar pustulosis. *J Eur Acad Dermatol Venereol.* 2018;32(5):e204-206.
7. Murakami M. Guselkumab for the treatment of palmoplantar pustulosis. *Expert Opin Biol Ther.* 2020;20(8):841-852.
8. Shah S, Nikam B, Kale M, Jamale V, Chavan D. Safety and efficacy profile of oral cyclosporine versus oral methotrexate versus oral acitretin in palmoplantar psoriasis - A hospital based prospective investigator blind randomized controlled comparative study [published online ahead of print, 2020 Dec 9]. *Dermatol Ther.* 2020;e14650. doi:10.1111/dth.14650
9. Haebich G, Kalavala M. Successful treatment of refractory palmoplantar pustulosis with apremilast. *Clin Exp Dermatol.* 2017;42(4):471-473.
10. Haller C, Cozzio A, von Kempis J, Rubbert-Roth A. Successful treatment of rituximab-associated palmoplantar pustulosis with apremilast in a patient with seropositive rheumatoid arthritis [published online ahead of print, 2020 May 22]. *J Clin Rheumatol.* 2020;10.1097
11. Adamo S, Nilsson J, Krebs A, et al. Successful treatment of SAPHO syndrome with apremilast. *Br J Dermatol.* 2018;179(4):959-962.
12. Mikhailitchenko, Amy L., et al. Eight-patient case series of palmoplantar pustulosis treated successfully with apremilast. *J Psoriasis Psoriatic Arthritis.* 2019 Jun. 4(1);7–10.
13. Carrascosa de Lome R, Conde Montero E, de la Cueva Dobao P. Refractory palmoplantar pustulosis.

AUTHOR CORRESPONDENCE

David Crasto DO

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

doi:10.36849/JDD.6135

November 2021 1257 Volume 20 • Issue 11

Copyright © 2021

Journal of Drugs in Dermatology

OnabotulinumtoxinA for Systemic Sclerosis-associated Raynaud's Phenomenon: A Multi-Institutional Study on Accessibility and Effectiveness

Bina Kassamali BA,[a,b,*] Sheena Desai BS,[a,c,*] Michelle S. Min MD MS,[a,b] Daniel R. Mazori MD,[a,b] Camila Villa-Ruiz MPH,[a,d] Kylee JB Kus,[a,e] BS Gabriela A. Cobos MD,[a,b] Joseph Merola MD MMSc[a,b,f] Avery LaChance MD MPH,[a,b,#] Ruth Ann Vleugels MD MPH MBA[a,b,#]

[a]Department of Dermatology, Brigham and Women's Hospital, Boston, MA
[b]Harvard Medical School, Boston, MA
[c]Tufts University School of Medicine, Boston, MA
[d]Ponce Health Sciences University, School of Medicine, Ponce, PR
[e]Oakland University William Beaumont School of Medicine, Rochester, MI
[f]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

[*]Denotes co-first authors
[#]Denotes co-senior authors

INTRODUCTION

Raynaud's phenomenon (RP), a common presenting symptom of systemic sclerosis (SSc), is a painful and debilitating condition of the digits caused by increased vascular reactivity.[1,2] Recurrent digital ulcers and critical ischemic events may result in osteomyelitis or necessitate partial amputations.[1] Despite this and RP's profound impact on quality of life (QOL), there are currently no Food and Drug Administration (FDA)-approved therapies to treat this condition.[1] Additionally, severe RP is often challenging to treat, and numerous agents may be required to adequately control disease.[3] Accumulating evidence demonstrates that onabotulinumtoxinA (Botox®) hand injections may be an effective treatment choice for refractory RP.[1,2,4-6] Herein, we present our experience with the accessibility and effectiveness of onabotulinumtoxinA for 51 patients with SSc-associated RP, making this the largest cohort of its kind to date.

Following Institutional Review Board exemption by Mass General Brigham, we conducted a retrospective study from two large academic institutions to determine the accessibility and effectiveness of onabotulinumtoxinA for SSc-associated RP. We identified patients with SSc-associated RP for whom insurance approval for onabotulinumtoxinA was attempted between 2014-2020. Data regarding success in insurance coverage, disease severity, impact on quality of life, previously failed therapies, and effectiveness for RP were collected.

51 patients for whom onabotulinumtoxinA was prescribed were identified and included in the study. The median number of previously failed therapies for RP was 3 (range: 0–10). 80% (41/51) of PAs were initially denied, the most common reason being "not covered for SSc/off-label use" (32/41, 78%). Among the patients who were initially denied coverage, 41% (17/41) ultimately acquired coverage after a median 37.5 days (range: 4–434). All of these 17 patients had private insurance (Figure 1). This contrasts with 0% (0/8) of Medicare patients who ultimately obtained insurance approval. In total, 53% (27/51) of patients ultimately received coverage. Although all patients (9/9) who had failed 6 or more therapies ultimately received onabotulinumtoxinA coverage, only 60% (26/43) of patients who failed between 2 and 5 therapies received coverage.

Decreased QOL was documented in 35% (18/51) of patients; among these patients, 39% (7/18) still failed to obtain coverage. 82% (42/51) of patients had documented tissue loss, defined as ulcers, autoamputation, and/or gangrene. Among these patients, 45% (19/42) were still ultimately denied coverage.

92% (34/37) of patients with documented tissue loss who ultimately received onabotulinumtoxinA (either via insurance approval [n=20] or via free supply [n=14]) showed improvement after onabotulinumtoxinA treatment. Furthermore, 82% (36/44) of all treated patients had sufficient benefit to warrant continued treatment.

This study highlights the challenges of prescribing off-label onabotulinumtoxinA, despite clinical effectiveness, for SSc-associated RP. Our results indicate that the vast majority of patients with documented tissue loss who received onabotulinumtoxinA showed improvement. While onabotulinumtoxinA is an

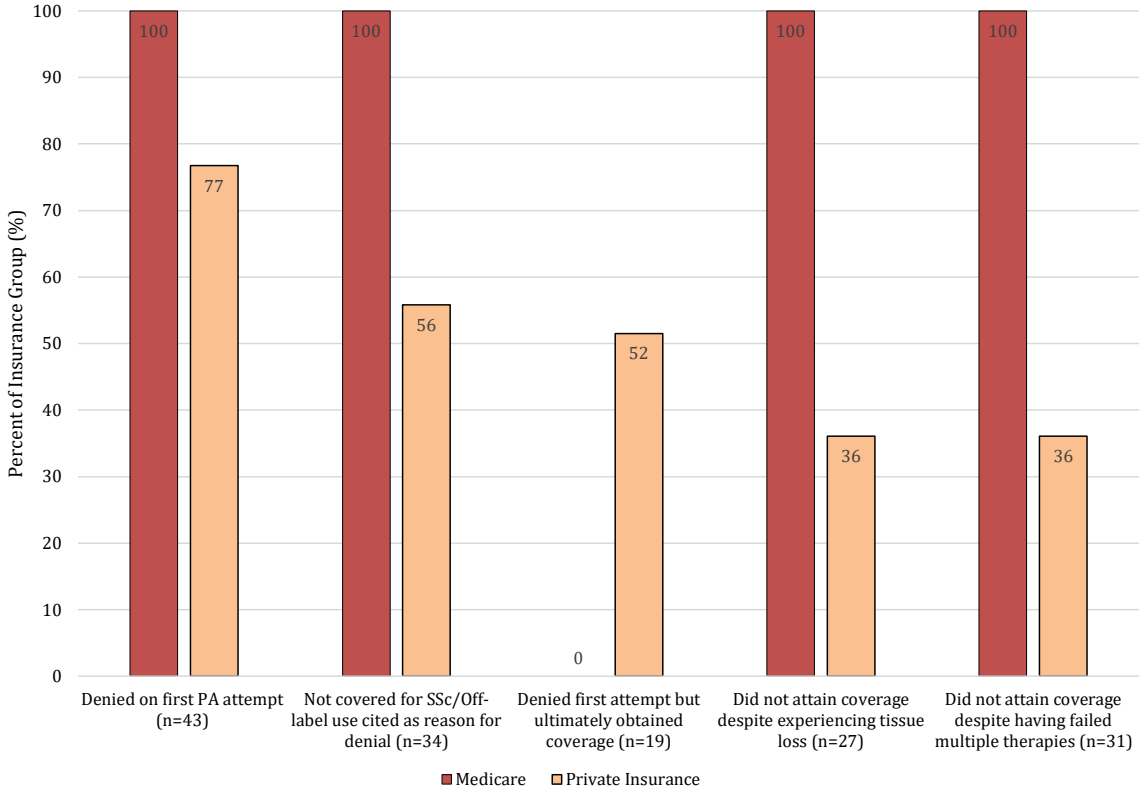
TABLE 1.

Coverage of OnabotulinumtoxinA for SSc-Associated RP According to Demographics, Clinical Features, and Treatment Response

	N (%)	Covered (%*)	Not Covered (%*)
Age (years)			
<21	N/A	--	--
21-30	N/A	--	--
31-40	3 (56)	3 (100)	0 (0)
41-50	9 (18)	5 (56)	4 (44)
51-60	19 (37)	12 (63)	7 (37)
61-70	14 (27)	5 (36)	9 (64)
71+	6 (12)	2 (33)	4 (67)
Gender			
Male	7 (14)	5 (71)	2 (29)
Female	44 (86)	22 (50)	22 (50)
Race			
White	41 (80)	20 (49)	21 (51)
Hispanic or Latino	3 (6)	2 (67)	1 (33)
Black or African American	2 (4)	1 (50)	1 (50)
Asian	1 (2)	1 (100)	0 (0)
Other	1 (2)	1 (100)	0 (0)
Not specified or unknown	3 (6)	2 (67)	1 (33)
Insurance			
Private or commercial	43 (84)	27 (63)	16 (37)
Medicare	8 (16)	0 (0)	8 (100)
Smoking Status			
Never Smoker	35 (69)	19 (54)	16 (46)
Former Smoker	14 (27)	8 (57)	6 (43)
Current Smoker	1 (2)	0 (0)	1 (100)
Unknown	1 (2)	0 (0)	1 (100)
Provider documented decreased QOL			
Yes	18 (35)	11 (61)	7 (39)
No	33 (65)	16 (48)	17 (52)
Tissue Loss			
Yes	42 (82)	23 (55)	19 (45)
No	7 (14)	2 (29)	5 (71)
Unknown	2 (4)	2 (100)	0 (0)
No. previously failed therapies			
0	1 (2)	0 (0)	1 (100)
1	5 (10)	3 (60)	2 (40)
2	9 (18)	3 (33)	6 (67)
3	10 (20)	7 (70)	3 (30)
4	9 (18)	5 (56)	4 (44)
5	6 (12)	2 (33)	4 (67)
6	2 (4)	2 (100)	0 (0)
7	3 (6)	1 (33)	2 (67)
8	2 (4)	2 (100)	0 (0)
9	1 (2)	1 (100)	0 (0)
10	1 (2)	0 (0)	1 (100)
Not specified or unknown	2 (4)	1 (50)	1 (50)
Tissue loss improvement after onabotulinumtoxinA			
Yes	34 (67)	20 (59)	14 (41)
No	3 (6)	2 (67)	1 (33)

*The percentages in covered vs. not covered use the N in column 2 as the denominator.

FIGURE 1. Summary of insurance coverage approval based on insurance type.



effective treatment for SSc-associated RP, this therapy remains an off-label use, and patients, particularly those with public health insurance, have limited success in acquiring insurance coverage for this treatment. This difference in coverage based on insurance status, despite treatment effectiveness, highlights an important access issue. Furthermore, there are no FDA-approved treatments for RP as it is an orphan disease, making it challenging to study in controlled clinical trials. Given the clinical benefits of off-label onabotulinumtoxinA for refractory SSc-associated RP, insurance approval should ideally not hinge on FDA approval alone. A reevaluation of the policies that determine coverage of therapies for RP is warranted.

DISCLOSURES

The authors have no conflicts of interest to declare.

REFERENCES

1. Dhaliwal K, Griffin MF, Salinas S, Howell K, Denton CP, Butler PEM. Optimisation of botulinum toxin type a treatment for the management of Raynaud's phenomenon using a dorsal approach: a prospective case series. *Clin Rheumatol.* 2019;38(12):3669-3676. doi:10.1007/s10067-019-04762-4
2. Jenkins SN, Neyman KM, Veledar E, Chen SC. A pilot study evaluating the efficacy of botulinum toxin A in the treatment of Raynaud phenomenon. *J Am Acad Dermatol.* 2013 Nov 1;69(5):834-5.
3. Herrick AL. Evidence-based management of Raynaud's phenomenon. *Ther Adv Musculoskelet Dis.* 2017 Dec;9(12):317-329. doi: 10.1177/1759720X17740074. Epub 2017 Nov 20. PMID: 29201156; PMCID: PMC5700788.
4. Frantz C, Avouac J, Distler O, et al. Impaired quality of life in systemic sclerosis and patient perception of the disease: A large international survey. *Semin Arthritis Rheum.* 2016;46(1):115-123. doi:10.1016/j.semarthrit.2016.02.005
5. Neumeister MW. Botulinum toxin type A in the treatment of Raynaud's phenomenon. *J Hand Surg.* 2010;35(12):2085–92. doi: 10.1016/j.jhsa.2010.09.019.
6. Neumeister MW, Chambers CB, Herron MS, Webb K, Wietfeldt J, Gillespie JN, et al. Botox therapy for ischemic digits. *Plast Reconstr Surg.* 2009;124(1):191–201. doi: 10.1097/PRS.0b013e3181a80576.
7. Sycha T, Graninger M, Auff E, Schnider P. Botulinum toxin in the treatment of Raynaud's phenomenon: a pilot study. *European journal of clinical investigation.* 2004;34(4):312–3. doi: 10.1111/j.1365-2362.2004.01324.x.

AUTHOR CORRESPONDENCE

Ruth Ann Vleugels MD MPH MBA
E-mail:..... rvleugels@bwh.harvard.edu

Current
Clinical Solutions
November 2021

The Evolving Management of Actinic Keratoses

Dillon Nussbaum BSc and Adam Friedman MD FAAD

George Washington School of Medicine and Health Sciences, Washington, DC

Distributed by
JOURNAL OF DRUGS IN DERMATOLOGY
JDD

Abstract Dermatologists agree that due to the risk of progression to non-melanoma skin cancer, the treatment of actinic keratoses is warranted, however no consensus exists on a preferred treatment modality. While cryotherapy is the most widely utilized treatment for actinic keratoses, the increasing understanding of field cancerization has revealed that this approach misses the forest for the trees so to speak. The pathophysiology and treatment of actinic keratoses (AK), from lesion-directed to field-directed, was expertly discussed in two continuing education webinars available at the *Journal of Drugs in Dermatology* online. The recorded sessions entitled, *Actinic Keratosis: Current Understanding of Pathophysiology and Therapeutic Targets* by Dr. Brian Berman, as well as *Actinic Keratosis: Therapeutic Options and Evolving Considerations* by Dr. James Q. Del Rosso stress the importance of increased utilization of topical field therapies to treat both clinically evident and subclinical AKs present in the adjacent regional skin. AK treatment commonly results in anticipated sequelae, depending on the modality used, including erythema, crusting, vesiculation, pustulation, and erosion, so emphasis should be placed on minimizing the magnitude and duration of adverse events while maximizing efficacy. Attention was paid to the newest addition to the topical field therapy armamentarium, tirbanibulin, a tubulin and Src kinase inhibitor, and its efficacy and safety were reviewed.

Introduction

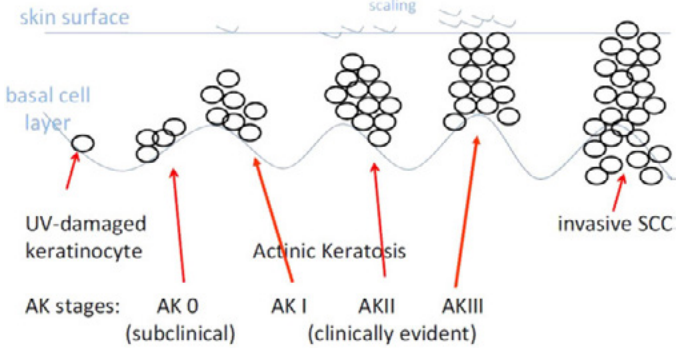
Playing whack-a-mole triggers a transient dopamine surge every time a participant hammers down one of the rodents, but no matter how much effort, the goal of clearing the board always seems to appear just out of reach—by design. Dermatologic practitioners have unwillingly found themselves playing a similar form of this game with actinic keratoses (AKs) when using lesion-directed therapies, especially in lighter skin patients with chronic sun exposure. AKs are rough erythematous papules resulting from significant ultraviolet radiation (UV) exposure and are associated with increased risk for development of non-melanoma skin cancer (NMSC), most notably squamous cell carcinoma (SCC). Prevalence of AKs in the US is 1.77% for patients between 50 and 59, 4.61% for patients between 60 and 69, 9.38% for patients between 70 and 79, and 14.57% for patients ≥80.[1]

The current understanding and therapies for AKs were skillfully discussed by Dr. Brian Berman, Co-Director of the Center for Clinical and Cosmetic Research and voluntary faculty of the Department of Dermatology and Cutaneous Surgery at the University of Miami during his continuing education webinar, *Actinic Keratosis: Current Understanding of Pathophysiology and Therapeutic Targets* available through the JDD online. Dr. Berman noted that the number of AKs a patient has is correlated with the risk of developing SCC such that someone with one-to-five AKs has a RR of 1.7 (0.4, 6.5), and someone with over twenty AKs has a RR of 11.0 (2.6, 46.6). One study examined a population of veterans to monitor what would happen if an AK was left without treatment and one year later 0.6% progressed to SCC compared to 2.57% after four years.[2,3] Few new entrants to the AK treatment arsenal have been approved in the past decade as Dr. James Q. Del Rosso, Research Director of JDR Dermatology Research in Las Vegas, Nevada and Senior Vice President of Clinical Research and Strategic Development at Advanced Dermatology and Cutaneous Surgery in Maitland, Florida, conveyed in his continuing education webinar, *Actinic Keratosis: Therapeutic Options and Evolving Considerations.* Drs. Berman and Del Rosso both reviewed tirbanibulin as the newest and possibly the most tolerable treatment for AKs.

Historically, clinicians only treated what they could see, also known as lesion-directed therapy, but more recently there has been a shift to a more comprehensive approach to address the entire area of actinic damage with field-directed therapies.[4]

To highlight the importance of this point, Dr. Berman referenced a study in which normal appearing skin between two clinically apparent AKs demonstrates histologic evidence of AK and therefore argued that, although not clinically evident, microscopic disease is present and could pose malignant potential.[5,6] Dr. Berman also cited a study that compared the incidence of various classifications of AKs in proximity to an SCC; intuitively one might consider that more clinically apparent AKs would be identified in perilesional biopsies of SCCs, however the authors determined that lower grade AK1s are found overlaying an SCC 63.8% of the time, compared to 17.9% for AK2s and 18.4% for AK3s (Figure 1).[7,8] Although a larger, scalier, and more eye catching AK may appear higher risk, these studies together argue that lower grade AKs and perilesional skin must not be forgotten during treatment.

Figure 1. The spectrum of AKs to SCC. AKs are graded histologically into three categories with AK3s most closely resembling SCCs. *Reprinted with permission from Dermatologic Therapy, by D. Kopera, 2020, p. 2. Copyright 2020 by Wiley.*



Drs. Berman and Del Rosso conveyed that data on field cancerization supports that perilesional skin of an AK is comparably at risk for mutations and dysplastic cells even if no clinical evidence is apparent visibly, even with a dermatoscope. Clinicians have for some time utilized field therapy with numerous and chronic AKs, often combining with lesion directed therapy.[3,5] The combination of lesion-directed and field therapies together has shown to provide more efficacious treatment of AKs and therefore prevention of SCCs.[9,10] However, the shift toward field therapy is happening far too slowly, in fact, one study found that from 2009–2016 50.8% office visits for AKs resulted in treatment with cryotherapy, and field therapy accounting for only 3.2%.[11] There is a need to increase awareness and utilization of field therapy for AKs in an effort to improve the standard of care and benefit to patients.

Pathophysiology of AKs

DNA repair mechanisms aim to prevent aberrant cells from proliferating and causing local tissue damage or even death. However, those mechanisms can falter with cumulative UV

exposure to keratinocytes throughout one's lifetime. Dr. Berman explained the pathophysiology of AKs and their transformation to SCC by describing that UV exposure increases oxidative stress, which initially causes a reversible mutation in the p53 tumor suppressor gene. Additional UV exposure then reversibly mutates the RAS proto-oncogene, which is crucial for cell growth, differentiation, and development. At this stage, a clinically apparent AK is likely present. Further UV exposure irreversibly mutates the p16 tumor suppressor gene, which is then characteristic of SCCs. This spectrum is correlated with disorganized hyperproliferation of keratinocytes and invasive SCC as a result. Many additional variables go into whether one is at risk for AKs including genetics, exposure, skin type, and those with existing defects in DNA repair enzymes, but mutations in p53, RAS, and p16 are among the most common and traceable along the progression to SCC[12,13] Drs. Berman and Del Rosso stressed the chronic nature of AKs and highlighted that effective treatment often requires repeated use of one or more therapies and that continued surveillance for malignancy is always warranted.

Therapeutic Options for AKs

Treatment for AKs includes photoprotective measures, chemopreventative supplements, as well as lesion-directed treatment and field therapy. Photoprotective measures include sensible avoidance, sunscreen, and protective attire. Polypodium leucotomas extract is a natural supplement with published safety data and appears to show some evidence of reducing UV induced damage, however, supplements in the US are not regulated by the FDA, so independent research is recommended for products containing polypodium leucotomas extract which are supported by recognized scientific data published in peer-reviewed literature.[14]

Drs. Berman and Del Rosso both emphasized that higher risk patients with prior skin cancers can benefit from chemoprevention with Vitamin B3, nicotinamide (NAM), 500mg twice daily. One study found NAM was associated with a 13% reduction in AKs, 23% reduction in NMSC, and 30% reduction in SCC as compared to the placebo group after one year. NAM works by replenishing NAD+ stores in the cell as well as inhibiting PARP-1 and sirtuins, which normally act to suppress p53 tumor suppressor gene. The study found a significant causal relationship between NAM and reducing skin cancer in those who have had one previously, but theoretically the mechanism would be similar in someone who is yet to have an AK or NMSC.[15,16]

Lesion-directed therapy is recommended for patients with few AKs and consists of cryotherapy, photodynamic therapy (PDT), and much less commonly, intralesional 5-fluourouracil (5-FU).

Cryotherapy rapidly freezes the exposed cells to subzero temperatures, usually with liquid nitrogen, which forms ice crystals in the cells and extracellular matrix effectively lysing the cells. Upon thawing, rapid shift in ions like calcium and potassium further damage the surviving and some adjacent cells.[17] While many assume cryotherapy is effective, one study found that AKs are 72% likely to recur in the same spot compared to 54% for topical 5-FU, and 73% for imiquimod.[18] Cryotherapy also poses the risk of dyspigmentation and scarring, especially in darker skin types.[19]

Dr. Berman mentioned that PDT is FDA approved as a lesion-directed therapy of AKs, but in practice, methyl aminolevulinic acid (MLA) or aminolevulinic acid (ALA) are generally applied to a field like the face or scalp. Dysplastic cells will selectively convert MLA or ALA into photoporphryin IX in their mitochondria during a brief incubation time. A blue or red light is then shined on the affected area for sixteen minutes and forty seconds and the photons are selectively absorbed by photoporphryin IX in the dysplastic cells that later undergo apoptosis.[19] LSRs from one large study with PDT include erythema in 89% of patients, crusting in 9% and pustules in 6%.[20,21]

5-FU is a thymidylate synthase inhibitor that acts as an antimetabolite stopping the growth of rapidly proliferating cells and is also directly cellular toxic. Intralesional 5-FU is effective against AKs and SCC, but due to its cellular toxicity 5-FU can cause marked pain, erythema, scaling, pruritus, and even necrosis. 5-FU is more commonly applied topically than intralesional due to the difficulty in treating the remaining field as well as the significantly associated adverse events associated with intralesional 5-FU including erythema, pustulation, and necrosis.[22]

Drs. Berman and Del Rosso agree that if that lesion-directed or field therapy do not resolve an AK, a biopsy should be considered as any lesion that has been treated with a less invasive modality multiple times without resolution has an increased risk for SCC. Benefits of a biopsy include diagnosing a possible SCC, regression of a remaining AK, or even revealing a different unexpected diagnosis.

Field therapy is recommended for patients who have numerous AKs such that lesion-directed therapy would be too numerous, painful, and not cost effective. Field cancerization argues that patients with one AK would benefit from topical field therapies, which consist of 5-FU, imiquimod, diclofenac, and now tirbanibulin. Each field therapy interestingly has a unique mechanism of action and therefore requires varying application durations, and subsequently varying intensity of adverse events. Some clinicians have reported success with chemical peeling agents and ablative lasers to treat and prevent AKs however these have not been FDA approved for this indication.[8]

5-FU, as discussed previously, is a toxic antimetabolite that stops growth of rapidly proliferating cells and must be applied once or twice daily for two-to-four weeks for full effect. The topical form has been approved in 0.5%, 0.1%, as well as 5% in creams and solutions. A recent study comparing four field therapies found that 5-FU performed the best at reducing total AKs such that 74.7% of patients achieved 75% reduction in AKs one year following treatment.[23] One study found that 0.5% 5-FU cream once daily was as effective as 5% 5-FU cream twice daily

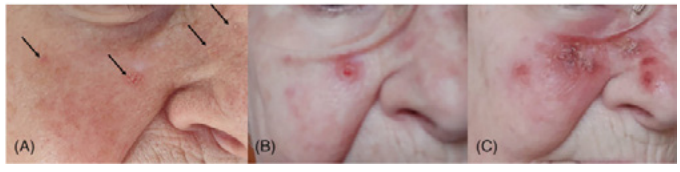
in percent reduction and total clearance of AKs. The same study found the lower concentration was more effective than the 5% cream in reducing AKs from baseline and suggested patients prefer the lower concentration.[24]

Ingenol mebutate induces a rapid influx of calcium followed by downstream effects of modulating protein kinase C in dysplastic cells. Ingenol mebutate was available in a gel vehicle as 0.015% and 0.05% concentrations and indicated to apply for 2–3 days. Phase 3 trials showed that after eight weeks 21.4% of patients were completely clear and 59.4% had a 75% reduction in AKs. One study compared the tolerability of 5% 5-FU against 0.015% ingenol mebutate, 5-FU applied twice weekly for four weeks and ingenol mebutate applied daily for three days and found comparable results. Ingenol mebutate commonly caused pain, erythema, scale, crusting, and pustulation among patients that peaked one week into treatment and resolved after two weeks on average. LSRs graded out of 24 peaked at a mean of 10.85 (+-3.12) and on day four, which resolved by day 15 on average. The local skin responses (LSRs) of ingenol mebutate was comparable to 5-FU, which scored 10.86 (+-3.55). However, LSR from 5-FU peaked on day 29, and resolved by day 36. This study should be assumed to have a lesser LSR than one in which 5-FU was applied more frequently as usually directed. However, ingenol mebutate was recently removed from most markets, including the United States, due to a variety of factors including concerns regarding increased risk of SCC. The European Medicine Agency, equivalent to the FDA, found in a three-year study of 484 patients, that 3.3% of developed SCC in the Ingenol Mebutate group versus 0.4% in the imiquimod group.[25,26,27]

Imiquimod is a toll-like receptor-7 agonist that amplifies the host immune response and stimulates apoptosis of dysplastic cells. Imiquimod is more selective for dysplasia rather than proliferating cells like 5-FU. This selectivity allows imiquimod to be more tolerable overall for most patients compared to 5-FU, however the adverse events are similar. Imiquimod is approved in 3.75% and 2.5% creams and phase 3 trials showed a 100% clearance in AKs among 35.6% and 30.6% of patients, respectively. 75% reduction in AKs was achieved by 59.4% and 48.1% of patients in the 3.75% and 2.5% concentration groups. LSRs were observed in almost all the patients during treatment course that consisted of once daily applications for two-week treatment intervals broken up by a two-week break. Erythema, crusting, and pustulation were observed most frequently by up to 25.2% and 13.8% of the stronger concentration and 14.4% and 9.4% of patients in the weaker concentration.[28,29] Figure 2 provides an example of AKs before and during treatment with imiquimod 3.75%.[8]

Diclofenac 3% gel is a nonsteroidal anti-inflammatory that inhibits cyclooxygenase-2, effectively reducing prostaglandin E2 and Bcl-2, which normally prevent apoptosis in dysplastic cells. In a phase 4 study, 41% of patients achieved 100% clearance of AKs and 78% achieved 75% reduction in AKs after 90 days. Adverse events were limited to mild application site reactions, itching, erythema, dry skin, exfoliation, localized edema, photosensitivity,

Figure 2. Example of LSRs to 3.75% imiquimod cream. (A) Eighty-seven-year-old female showing small erythematous scaly lesions on her right cheek (arrows). (B) Inflammatory reaction starting from day 3 of treatment with topical imiquimod 3.75% cream. (C) Day 14, end of treatment phase, showing field cancerization. *Reprinted with permission from Dermatologic Therapy, by D. Kopera, 2020, p. 2. Copyright 2020 by Wiley.*



and paresthesia. Diclofenac has the most tolerable side effect profile due to the slow extended duration of use but poses a compliance risk as it must be applied twice daily for sixty to ninety days.[30]

The most recent FDA-approved topical therapy for AK treatments, tirbanibulin 1% ointment, inhibits tubulin polymerization and halts the cell cycle selectively in proliferating cells, resulting in augmented apoptosis of dysplastic cells that form AK lesions. Tirbanibulin also disrupts Src kinase, which is crucial for cellular growth, division, and proliferation. These mechanisms allow tirbanibulin to act as a potent anti-proliferative and pro-apoptotic agent without any direct cellular toxicity that intensifies inflammation through marked cytokine release (such as observed with 5-FU application). Most importantly, clinical trial data supports use of tirbanibulin over a short five-day course of application with demonstration of efficacy on follow-up. The LSRs associated with tirbanibulin use were shown to exhibit a low magnitude and relatively short duration of erythema, crusting, erosion, and discomfort, especially when considering LSRs observed with other topical field therapies. LSRs for tirbanibulin were measured on an 18-point scale, rather than the 24-point scale in references above. In the pivotal trials with tirbanibulin, LSRs peaked at day 8, decreased through day 15, and resolved by day 28 in the majority of cases. Compared to other field therapies, the onset of LSRs appears less intense and more manageable for patients. Drs. Berman and Del Rosso presented phase 3 studies that revealed 100% complete clearance of AKs in 44–54% of patients 57 days following treatment with tirbanibulin. 68–76% of patients achieved ≥ 75% reduction in AKs. The pooled median percent reduction in lesion count was 87.5%. In patients with complete clearance, presence of AKs in the treatment field were noted in 47% of patients at one year, showing that a single 5-day course of topical tirbanibulin sustained suppression of AKs in the treatment in a large number of patients without use of any other topical or field-directed AK therapy. The short 5-day duration of treatment combined with both efficacy and favorable tolerability are likely to attract increasing numbers of clinicians and patients to the use of tirbanibulin, which was echoed by both presenters.[31]

Dr. Berman discussed future directions in treating AKs and presented a study combining calcipotriol with 5-FU that enhanced the efficacy in treating AKs by inducing thymic stromal lymphopoietin and recruiting local CD4+ T cells to the region.[32]

Treating AKs satisfactorily necessitates a multifaceted approach and patient-applied topical field therapies that require fewer applications and pose fewer risks are invaluable. With the addition of tirbanibulin to the arsenal of AK therapies, clinicians can reduce the multiple adverse sequelae that AKs cause including progression to skin cancer.

Disclosure

This work is supported by an independent medical education grant from Almirall, LLC.

Author Correspondence

Adam Friedman MD FAAD
ajfriedman@mfa.gwu.edu

References

1. Yaldiz M. (2019). Prevalence of actinic keratosis in patients attending the dermatology outpatient clinic. *Medicine*, 98(28), e16465.
2. Green A, Battistutta D. (1990). Incidence and determinants of skin cancer in a high-risk australian population. *International Journal of Cancer,* 46(3), 356–361.
3. Criscione VD, Weinstock MA, Naylor MF, et al and the Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group. (2009). Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer,* 115(11), 2523–2530.
4. Asche CV, Zografos P, Norlin JM, et al. (2016). Evaluation of resource utilization and treatment patterns in patients with actinic keratosis in the United States. *Value in Health:* the journal of the International Society for Pharmacoeconomics and Outcomes Research, 19(2), 239–248.
5. Markowitz O, Schwartz M, Feldman E, et al. (2016). Defining field cancerization of the skin using noninvasive optical coherence tomography imaging to detect and monitor actinic keratosis in ingenol mebutate 0.015%- treated patients. *J Clin Aesthet Dermatol,* 9(5), 18–25.
6. Cornejo CM, Jambusaria-Pahlajani A, Willenbrink TJ, et al. Field cancerization: Treatment. *J Am Acad Dermatol.* 2020 Sep;83(3):719-730. Epub 2020 May 6. PMID: 32387663.
7. Fernández-Figueras MT, Carrato C, Sáenz X, et al (2015). Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. *J Acad Dermatol Venereol,* 29(5), 991–997.
8. Kopera D. (2020). Earliest stage treatment of actinic keratosis with imiquimod 3.75% cream: Two case reports-perspective for non melanoma skin cancer prevention. *Dermatologic Therapy,* 33(4), e13517.
9. Piquero-Casals J, Morgado-Carrasco D, Gilaberte Y, et al (2020). Management pearls on the treatment of actinic keratoses and field cancerization. *Dermatology and Therapy,* 10(5), 903–915.
10. Held L, Eigentler TK, Leiter U, Garbe C, Berneburg MJ. (2013). Effective combination of photodynamic therapy and imiquimod 5% cream in the treatment of actinic keratoses: three cases. *BioMed Research International,* 2013, 102698.
11. Ranpariya VK, Muddasani S, Mahon AB, Feldman SR. (2021). Frequency of procedural and medical treatments of actinic keratosis. *J Am Acad Dermatol,* S0190-9622(21)00598-3. Advance online publication.
12. Bagazgoitia, L, Cuevas J, Juarranz A. (2010). Expression of p53 and p16 in actinic keratosis, bowenoid actinic keratosis and Bowen's disease. *J Eur Acad Dermatol Venereol,* 24(2), 228–230.
13. Oberholzer PA, Kee D, Dziunycz P, et al. (2012). RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. *Am J Clin Oncol,* 30(3), 316–321.
14. Berman B, Ellis, C, Elmets C. (2016). Polypodium leucotomos–an overview of basic investigative findings. *J Drugs Dermatol,* 15(2), 224–228.
15. Chen AC, Martin AJ, Choy B, et al (2015). A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *New Engl J Med,* 373(17), 1618–1626.
16. Starr P. (2015). Oral nicotinamide prevents common skin cancers in high-risk patients, reduces costs. *American Health & Drug Benefits,* 8(Spec Issue), 13–14.
17. Goldenberg G, Perl M. (2014). Actinic keratosis: update on field therapy. *J Clin Aesthet Dermatol,* 7(10), 28–31.
18. Krawtchenko N, Roewert-Huber J, Ulrich M, et al (2007). A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol,* 157 Suppl 2, 34–40.
19. Cook DK, Georgouras K. (1994). Complications of cutaneous cryotherapy. *The Medical Journal of Australia,* 161(3), 210–213.
20. Goldman M, Atkin D. (2003). ALA/PDT in the treatment of actinic keratosis: spot versus confluent therapy. *J Cosmet Laser Ther,* 5(2), 107–110.
21. Prince GT, Cameron MC, Fathi R, Alkousakis T. (2018). intralesional and laser-assisted 5-fluorouracil in dermatologic disease: a systematic review. *J Drugs Dermatol,* 17(3), 274–280.
22. Lehmann P. (2007). Nebenwirkungen der topischen photodynamischen Therapie [Side effects of topical photodynamic therapy]. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete,* 58(7), 597–603. https://doi.org/10.1007/s00105-007-1363-4
23. Jansen M, Kessels J, Nelemans PJ, et al. (2019). Randomized Trial of Four Treatment Approaches for Actinic Keratosis. *New Engl J Med,* 380(10), 935–946.
24. Loven K, Stein L, Furst K, Levy S. (2002). Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. *Clinical Therapeutics,* 24(6), 990–1000.
25. Samorano LP, Torezan LA, Sanches JA. (2015). Evaluation of the tolerability and safety of a 0.015% ingenol mebutate gel compared to 5% 5-fluorouracil cream for the treatment of facial actinic keratosis: a prospective randomized trial. *J Eur Acad Dermatol Venereol,* 29(9), 1822–1827.
26. Hanke CW, Albrecht L, Skov T, et al. (2020). Efficacy and safety of ingenol mebutate gel in field treatment of actinic keratosis on full face, balding scalp, or approximately 250 cm2 on the chest: A phase 3 randomized controlled trial. *J Am Acad Dermatol,* 82(3), 642–650.
27. (2020) EMA suspends Picato as a precaution while review of skin cancer risk continues. *European Medicine Agency.* EMA/32231/2020, 1-2.
28. Swanson N, Smith CC, Kaur M, Goldenberg G. (2014). Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: two phase 3, multicenter, randomized, double-blind, placebo-controlled studies. *J Drugs Dermatol,* 13(2), 166–169.
29. Swanson N, Abramovits W, Berman B, et al. (2010). Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol,* 62(4), 582–590.
30. Nelson C, Rigel D, Smith S, et al. (2004). Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). *J Drugs Dermatol,* 3(4), 401–407.
31. Blauvelt A, Kempers S, Lain E, et al and Phase 3 Tirbanibulin for Actinic Keratosis Group (2021). Phase 3 trials of tirbanibulin ointment for actinic keratosis. *New Engl J Med,* 384(6), 512–520.
32. Cunningham TJ, Tabacchi M, Eliane JP, et al. (2017). Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Investig,* 127(1), 106–116.
33. Lozzi F, Lanna C, Mazzeo M, et al. (2019). Investigational drugs currently in phase II clinical trials for actinic keratosis. *Expert Opin Investig Drugs,* 28(7), 629–642.
34. Kopasker D, Kwiatkowski A, Matin RN, et al. (2019). Patient preferences for topical treatment of actinic keratoses: a discrete-choice experiment. *Br J Dermatol,* 180(4), 902–909.
35. Berry K, Butt M, Kirby JS. (2017). influence of information framing on patient decisions to treat actinic keratosis. *JAMA Dermatol,* 153(5), 421–426.

To learn more about this topic, please watch two recent continuing education webinar series on the JDD online, supported by an independent medical education grant provided by Almirall, LLC.

Dr. Berman's webinar:
https://jddonline.com/actinic-keratosis-current-understanding-of-pathophysiology-and-therapeutic-targets

Dr. Del Rosso's webinar:
https://jddonline.com/actinic-keratosis-therapeutic-options-and-evolving-considerations

UNITED STATES POSTAL SERVICE®

Statement of Ownership, Management, and Circulation (Requester Publications Only)

1. Publication Title	2. Publication Number	ISSN	3. Filing Date
PHYSICIANS CONTINUING EDUCATION CORP/ JOURNAL OF DRUGS IN DERMATOLOGY	25376	15459616	9/27/2021
4. Issue Frequency	**5. Number of Issues Published Annually**		**6. Annual Subscription Price** *(if any)*
MONTHLY	12		$300.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*
115 E 23RD ST FL 3
NEW YORK, NY 10010-4565

Contact Person: NICK GILLESPIE
Telephone *(Include area code)*: (646) 453-5711

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
115 E 23RD ST
3RD FLOOR UNIT 322
NEW YORK, NY 10010-4565

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
Shelley Tanner
115 E 23rd St
3rd Floor Unit 322
New York, NY 10010-4565

Editor *(Name and complete mailing address)*
Perry Robins
115 E 23rd St
3rd Floor Unit 322
New York, NY 10010-4565

Managing Editor *(Name and complete mailing address)*
Nick Gillespie
115 E 23rd St
3rd Floor Unit 322
New York, NY 10010-4565

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Lawrence Robins	115 E 23rd St, 3rd Floor Unit 322, New York, NY 10010-4565
Shelley Tanner	115 E 23rd St, 3rd Floor Unit 322, New York, NY 10010-4565

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box. → ☒ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☒ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement.)*

13. Publication Title	14. Issue Date for Circulation Data Below
PHYSICIANS CONTINUING EDUCATION CORP/ JOURNAL OF DRUGS IN DERMATOLOGY	9/1/2021

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
a. Total Number of Copies *(Net press run)*			13,432	13,252
b. Legitimate Paid and/or Requested Distribution *(By mail and outside the mail)*	(1)	Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. *(Include direct written request from recipient, telemarketing, and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)*	9,237	9,504
	(2)	In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. *(Include direct written request from recipient, telemarketing, and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)*		
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid or Requested Distribution Outside USPS®		
	(4)	Requested Copies Distributed by Other Mail Classes Through the USPS (e.g., First-Class Mail®)	21	21
c. Total Paid and/or Requested Circulation *(Sum of 15b (1), (2), (3), and (4))* ▶			9,258	9,525
d. Non-requested Distribution *(By mail and outside the mail)*	(1)	Outside County Nonrequested Copies Stated on PS Form 3541 *(include sample copies, requests over 3 years old, requests induced by a premium, bulk sales and requests including association requests, names obtained from business directories, lists, and other sources)*	4,059	3,623
	(2)	In-County Nonrequested Copies Stated on PS Form 3541 *(include sample copies, requests over 3 years old, requests induced by a premium, bulk sales and requests including association requests, names obtained from business directories, lists, and other sources)*		
	(3)	Nonrequested Copies Distributed Through the USPS by Other Classes of Mail *(e.g., First-Class Mail, nonrequestor copies mailed in excess of 10% limit mailed at Standard Mail® or Package Services rates)*		
	(4)	Nonrequested Copies Distributed Outside the Mail *(Include pickup stands, trade shows, showrooms, and other sources)*	0	0
e. Total Nonrequested Distribution *[Sum of 15d (1), (2), (3) and (4)]*			4,059	3,623
f. Total Distribution *(Sum of 15c and e)* ▶			13,317	13,148
g. Copies not Distributed *(See Instructions to Publishers #4, (page #3))* ▶			115	104
h. Total *(Sum of 15f and g)*			13,432	13,252
i. Percent Paid and/or Requested Circulation *(15c divided by 15f times 100)* ▶			69.52%	72.44%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

UNITED STATES POSTAL SERVICE®

Statement of Ownership, Management, and Circulation (Requester Publications Only)

16. Electronic Copy Circulation	Average No. Copies Each Issue During Previous 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Requested and Paid Electronic Copies ▶		
b. Total Requested and Paid Print Copies (Line 15c) + Requested/Paid Electronic Copies (Line 16a) ▶		
c. Total Requested Copy Distribution (Line 15f) + Requested/Paid Electronic Copies (Line 16a) ▶		
d. Percent Paid and/or Requested Circulation (Both Print & Electronic Copies) (16b divided by 16c × 100) ▶		

☒ **I certify that 50% of all my distributed copies (electronic and print) are legitimate requests or paid copies.**

17. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the 11/1/2021 issue of this publication.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: Shelley N. Tanner — Date: 9/28/2021

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS

DELIVERING SOON!

The JDD team and the Welcome Kit Sponsors are proud to support the JDD Welcome Kit as a graduation gift to the 2021 Dermatology Residency Graduates! This kit is a toolbox of samples and information that allows young dermatologists to test products first-hand and is designed to be instrumental in introducing new graduates to the community as they embark on their dermatology career.

LA ROCHE-POSAY LABORATOIRE DERMATOLOGIQUE
CeraVe DEVELOPED WITH DERMATOLOGISTS
SkinCeuticals ADVANCED PROFESSIONAL SKINCARE
NUTRAFOL®
GALDERMA EST. 1981
REVISION SKINCARE®
Aveeno HEALTHY. IT'S OUR NATURE.
Neutrogena®
NEOSTRATA® THE SCIENCE OF SKIN REGENERATION
VICHY LABORATOIRES

BUILT BY NATURE.
BACKED BY SCIENCE.

REBALANCE THE SKIN MICROBIOME.
REDUCE ATOPIC DERMATITIS SYMPTOMS.

LIPIKAR BALM AP+ IS CLINICALLY PROVEN TO HELP RESTORE SKIN BARRIER FUNCTION.

50% fewer flare-ups[3] **33%** less staph[3] **47%** less itchiness[4]

than a competitive moisturizer after using a prescription treatment

Dermatologist-tested | Allergy-tested | Fragrance-free | Paraben-free | Non-comedogenic

REFERENCES: 1. Baldwin HE, Bhatia ND, Friedman A, Eng RM, Seité S. The role of cutaneous microbiota harmony in maintaining a functional skin barrier. *J Drugs Dermatol.* 2017;16(1):12-18. **2.** Mahe YF, Perez MJ, Tacheau C, et al. A new Vitreoscilla filiformis extract grown on spa water-enriched medium activates endogenous cutaneous antioxidant and antimicrobial defenses through a potential toll-like receptor 2/protein kinase C, zeta transduction pathway. *Clin Cosmet Investig Dermatol.* 2013;6:191-196. **3.** Seité S, Zelenkova H, Martin R. Clinical efficacy of emollients in atopic dermatitis patients–relationship with the skin microbiota modification. *Clin Cosmet Investig Dermatol.* 2017;10:25-33. **4.** Data on file. L'Oréal. Evaluation of tolerance and efficacy of a new moisturizer in children with atopic dermatitis.

All other product/brand names and/or logos are trademarks of the respective owners.
La Roche-Posay ©2021

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE