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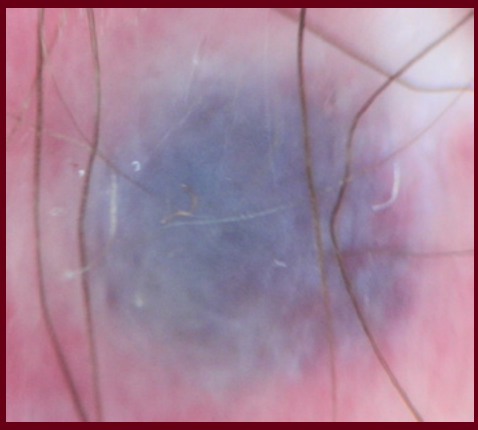
JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS



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

ANTI-AGING · AESTHETIC · MEDICAL DERMATOLOGY

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.

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

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Journal of Drugs in Dermatology

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JDD
DRUGS • DEVICES • METHODS

JOURNAL OF DRUGS IN DERMATOLOGY

ORIGINAL ARTICLES

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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.

LA ROCHE-POSAY
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BRIEF COMMUNICATIONS

LETTERS TO THE EDITOR

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Topical Stabilized Cysteamine as a New Treatment for Hyperpigmentation Disorders: Melasma, Post-Inflammatory Hyperpigmentation, and Lentigines

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[b]Skin Wellness Dermatology, Birmingham, AL

[c]Vitiligo and Pigmentation Institute of Southern California, Los Angeles, CA

[d]Global Medical Director, Scientis, Trinity, FL

ABSTRACT

Cysteamine is an aminothiol naturally present in cells of the human body as an antioxidant resulting from the degradation of Coenzyme A. Physiologically it is well distributed in mammalian tissues. Highly concentrated in human milk, cysteamine acts as an intrinsic antioxidant and is known for its protective role. Multiple studies now document that cysteamine is a potent skin depigmenting agent. Historically, its rapid oxidation and very offensive odor made it difficult for topical use until recently when stabilization of cysteamine was achieved. This has led to an acceptable galenical form for topical application. Since 2015, the efficacy, safety, and tolerability of stabilized cysteamine (st.Cys) has been demonstrated in multiple clinical studies, as well a case reports. Stabilized cysteamine has demonstrated significant effectiveness for the treatment of melasma by two double-blind randomized and vehicle control trials. Stabilized cysteamine has shown to be as effective as well-known depigmenting therapies, including triple combination cream or tranexamic acid mesotherapy, with higher tolerability. A recent clinical trial has shown considerable efficacy of topical cysteamine for the treatment of senile lentigines, which are usually considered to be resistant to topical depigmenting agents. Topical stabilized cysteamine can be regarded to as one of the most potent treatments available for hyperpigmentation disorders in humans.

J Drugs Dermatol. 2021;20(12):1276-1279. doi:10.36849/JDD.6367

INTRODUCTION

Cysteamine is an aminothiol naturally present in cells of the human body as an antioxidant resulting from the degradation of Coenzyme A.[1] Physiological levels are well distributed in mammalian tissues. Highly concentrated in human milk, cysteamine acts as an intrinsic antioxidant and is known for its protective role.[2] It was originally evaluated in the 1950s for its protection properties against ionizing radiation and in the 1970s for the treatment of cystinosis.[3,4] Today it is still the first and only drug approved by the FDA for this orphan disease.[5] As a potent antioxidant, cysteamine is known to be one of the most potent depigmenting agents available. This has been confirmed through several in vivo animal studies over the past few decades.[6,7] Other animal studies have verified it to have significantly higher efficacy as a depigmenting agent when compared to hydroquinone in vivo.[8,9] However, due to a very offensive odor and rapid oxidation, the use of cysteamine as a topical treatment was postponed until recent years, when its stabilization was achieved leading to an acceptable formulation for topical application (stabilized-cysteamine-5% cream).[10] In 2015 this formulation was proven to be effective for the treatment of melasma.[11] Since then, new hyper-pigmentary uses for topical stabilized cysteamine (st.Cys) have emerged following its demonstrated efficacy in multiple clinical studies and case reports. In this review, we will discuss clinical efficacy, safety and tolerability of st.Cys in the treatment of different skin hyperpigmentation disorders such as melasma, post-inflammatory hyperpigmentation, and lentigines.

Depigmenting Mechanism of Action of Thiols

Cysteamine is an aminothiol and its method of depigmenting action is not yet fully understood.

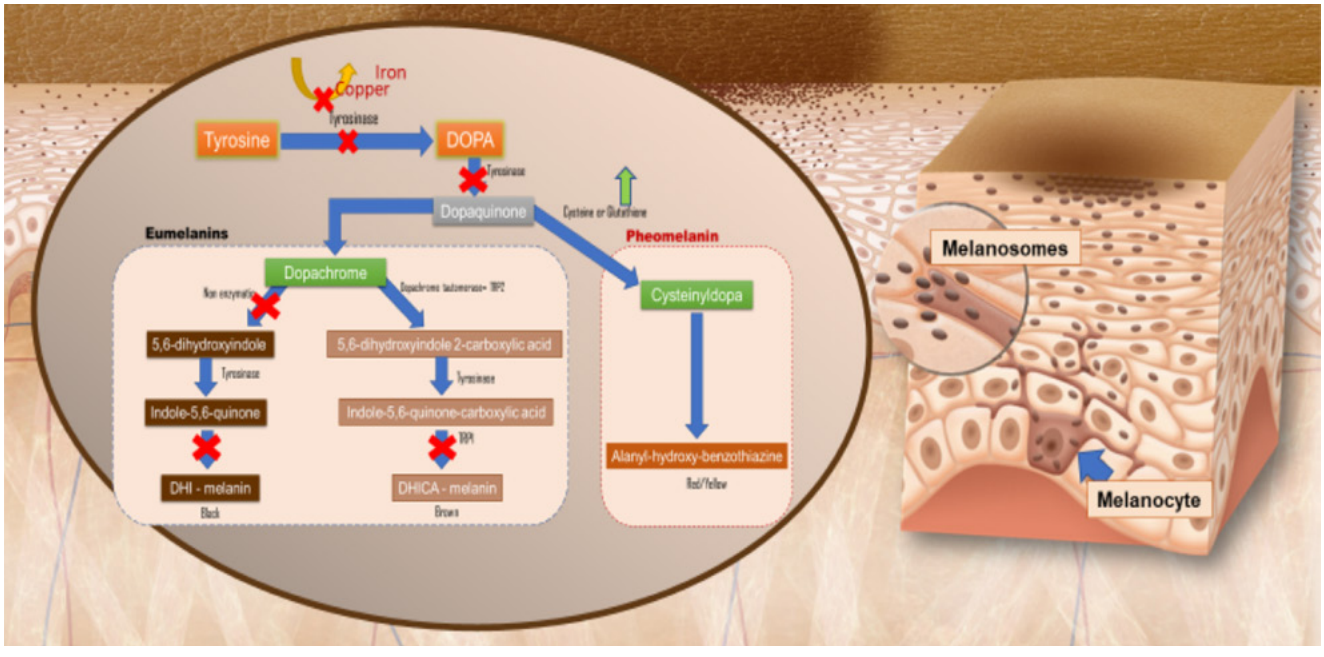
Some thiol molecules are known to inhibit tyrosinase and peroxidase, essential enzymes in the melanogenesis pathway leading to the conversion of tyrosine into dopaquinone, and the polymerization of indoles into melanin, respectively (Figure 1).[12]

As a copper and iron ion chelating agent, it is suggested that cysteamine could slow down the conversion of Tyrosine into dopaquinone, by preventing Fenton-type reactions.[13,14]

Thiols can also increase levels of intracellular glutathione, amplifying natural depigmenting effects.[14,15]

As a known antioxidant, cysteamine quenches hydroxy free radicals.[16] Antioxidant agents play a key role in the inhibition

FIGURE 1. Potential depigmenting mechanism for topical aminothiol agents.



of the melanogenesis pathway since most of the steps of this pathway are, in fact, oxidation reactions that are suppressed by antioxidant molecules. Prevention of direct photooxidation of pre-existing melanin by free radicals and by lightening dark melanin of the superficial skin cell layers are other depigmenting mechanisms of antioxidants.[17]

Cysteamine also seems to exhibit a keratolytic effect on the epidermis and is known to be a potent reducing agent used in hair perm products, which break hair keratin disulfide bonds when used in certain pH conditions.[18,19]This bond breaking effect is a property of keratolytic agents that are commonly used in the cosmetic industry, such as urea or alpha-hydroxy-acids (AHA).[20] Keratolytic agents such as tretinoin or glycolic acid are widely used in the management of hyperpigmentation disorders as they enhance the removal of superficial epidermal layers containing melanin and accelerate epidermal turnover.[17, 21]

In summary, there are several possible mechanisms in which cysteamine exhibits its effects on the skin. These may include five possible actions on the melanogenesis pathway: (i) enzymatic effect, (ii) iron chelation, (iii) glutathione cascade impeding effect, (iv) antioxidant, and (v) keratolytic effect.[11]

Cysteamine for the Treatment of Melasma

Melasma, also regularly referred to as "chloasma" or "mask of pregnancy", is a chronic acquired skin hyperpigmentation disorder. It is characterized by irregular brown macules symmetrically distributed, particularly on the face. It affects mainly women, specifically those with skin of color and more pigmented Fitzpatrick phenotypes (III–V). Melasma prevalence is estimated to be about 1% in the general population but can vary from 5% to 20% in higher risk-populations (eg, Brazil, US Latino community, Saudi Arabia).[22, 23]

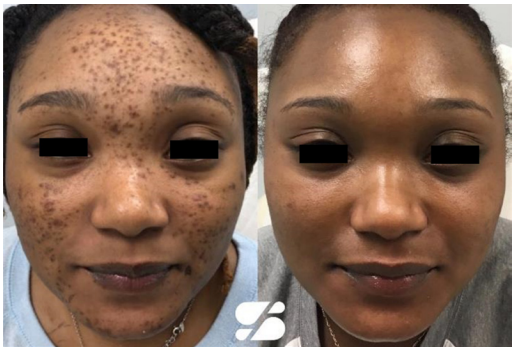
vs Placebo

Stabilized cysteamine has demonstrated significant efficacy for melasma in two double-blind, randomized, vehicle-controlled trials.[11, 24]

In the first study, 50 female melasma patients were randomly assigned to either of two groups of 25 to be treated with either st.Cys 5% or placebo vehicle. Both at month 2 and month 4, stabilized cysteamine was shown to produce significantly greater reductions in modified Melasma Area Severity Index (mMASI) (41.8%, 58.1%) and in melanin index measured by Mexameter (47.2%, 65.1%) compared to placebo vehicle mMASI reduction (7.1%, 10.8%) and melanin index reduction (7.4%, 11.9%).[11]

In the second study, 40 melasma patients were enrolled and randomly assigned to either of two groups, st.Cys 5% or placebo vehicle. Efficacy of st.Cys was evaluated through Dermacatch® and Mexameter® melanin index, MASI scores, Investigator Global Assessments (IGAs), and patient questionnaires, at baseline, 2-month, and 4-month. After 4 months, MASI scores were significantly reduced in the cysteamine group versus placebo (8.03 ± 5.2 vs 12.2 ± 7.4, P= 0.04, corresponding to a

FIGURE 2. Comedonal acne and post inflammatory hyperpigmentation treated with cysteamine 5% cream applied once daily for 15 minutes.



Before After 12 Weeks

decrease of 55.6% vs 7.6%). Mexameter and Dermacatch melanin index were also reduced after 4 months, resulting in a reduction of 59.2% (vs 10% for placebo) for Mexameter index and a reduction of 63.6% (vs 5.5%) for Dermacatch. In this study, 55% of the patients treated with st.Cys observed a moderate improvement of their melasma according to IGA.[24]

vs Modified Kligman Formula (mKF)

Compared to mKF, the gold standard treatment of melasma, st.Cys 5% was proven to be significantly more effective and more tolerable.

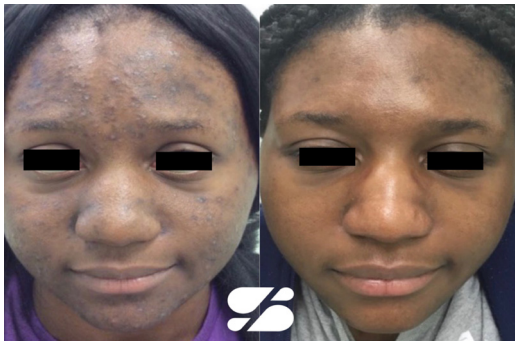
In an investigator initiated double-blind study 50 female melasma patients were randomly assigned to either of two groups, st.Cys 5% or mKF. At both week 8 and week 16, st.Cys 5% produced significantly greater reductions from baseline in modified Melasma Area Severity Index (mMASI) (32.3%, 51.3%), compared to mKF (23.7%, 42.3%; *P*=.005 and .001, respectively). Investigator global assessment and patient self-assessment scores were equivalent for both treatments at week 8 and week 16. All 64% of patients treated with st.Cys 5% reported no skin irritation, whereas only 8% of patients treated with mKF reported no skin irritation.[22]

Additionally, st.Cys 5% was reported to be effective in a patient with melasma who was recalcitrant to Kligman's formula and suffered ochronosis.[26] Daily 15-minute short-contact application of st.Cys 5% led to a reduction in MASI scores at months 2 and 4 months with a removal of the ochronosis. Remission was maintained using biweekly application after the 4 months.

vs Hydroquinone (HQ)

Two studies compared st.Cys 5% to HQ 4%.[27,28] In an investigator-driven, double-blinded trial, 20 female melasma patients were randomly assigned to st.Cys 5% or HQ4%. Stabilized cysteamine was shown to be superior in mMASI score reduction compared to HQ4% when analyzed as per protocol: the reduction in mMASI score was 39.1% (3.1 ±1.9) in the st.Cys 5% group and 33% (3.2 ± 3.7) in the HQ4% group (*P*=0.96).[27]

FIGURE 3. Post inflammatory hyperpigmentation from acne with some hypopigmentation treated with cysteamine 5% cream applied once daily for 15 minutes.



Before After 12 Weeks

The other study did not use the formulation of st.Cys 5% tested in all clinical studies to date but rather an alternative cysteamine formulation (Clarité® from Dermage), which had not been studied. When analyzed, this formulation showed 0.56% rather than 5% cysteamine concentration stated on the product. This degraded formulation shows inferior performance to HQ 4% in decreasing mMASI.[28,29]

vs Tranexamic Acid (TXA) Mesotherapy

When compared to the physician administered mesotherapy of TXA, st.Cys 5% was shown to be as effective and better tolerated than TXA mesotherapy for the treatment of melasma.

This independent, investigator initiated study evaluated 54 subjects randomized in two parallel groups, treated with either st.Cys 5% for 16 weeks or in-office TXA mesotherapy (0.05 mL) every 4 weeks for 3 sessions. The degree of improvement of mMASI reduction was 45.9% for st.Cys 5% after 16 weeks and 47.1% for multiple sessions of TXA mesotherapy. Both groups did not have recurrence of melasma in the follow-up period (8 weeks for TXA group and 16 weeks for st.Cys group). However, adverse events, such as irritation, burning sensation or erythema were significantly more frequent in the TXA mesotherapy group.[30]

Multiple case studies have also been published on the efficacy and safety of cysteamine in combination with laser treatment such as 1064nm Nd:YAG, and microdermabrasion.[31]

Cysteamine also exhibited efficacy in acquired pigmentary disorders caused by inflammation such as post-inflammatory hyperpigmentation and possible burnt-out morphea.[32,33]

Cysteamine for Lentigines and Facial Aging Dyschromia

Solar lentigines are common hyperpigmented lesions associated with negative psychological effects in individuals who are affected.[23] Topical depigmenting products are usually ineffective for the treatment of lentigines as well. Lentigines are also usually resistant to potent depigmenting formulas such as

Triple Combination, as revealed by Dr. Kligman.[34]

The first vehicle-controlled, double-blind randomized study assessing the efficacy of st.Cys 5% on solar lentigines is about to be published. It revealed significant improvement of solar lentigines after 12 weeks by all evaluation methods. Stabilized cysteamine represents a highly effective topical treatment for solar lentigines and can be considered as one of the first topical therapies effective for this hyperpigmentary disorder.

Additional unpublished case studies of st.Cys 5% reported significant improvement of facial aging dyschromia.

CONCLUSION

The above studies showed that cysteamine is and continues to be the subject of extensive clinical research in dermatology for treating hyperpigmentation disorders. Even if the physiological mechanism of action for reducing skin pigmentation of cysteamine is not fully understood, there is clear clinical evidence in humans that stabilized cysteamine is an effective and well tolerated treatment that can be considered as a first line non-hydroquinone treatment for hyperpigmentation disorders.

DISCLOSURES

Sana Shah PharmD is an employee of Scientis.

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An IL-23 inhibitor for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy[1]

NOTHING IS EVERYTHING

Nothing less than the opportunity for durable skin clearance.[1] | For your patients, **that's everything.**

SKYRIZI EFFICACY AT WEEK 16 IN TWO PIVOTAL PHASE 3 STUDIES (NRI)[2]

	CO-PRIMARY ENDPOINTS (*P*<0.0001)				SECONDARY ENDPOINT (*P*<0.001)	
	PASI 90 at Week 16		sPGA 0/1 at Week 16		PASI 100 at Week 16	
	ULTIMMA-1	ULTIMMA-2	ULTIMMA-1	ULTIMMA-2	ULTIMMA-1	ULTIMMA-2
SKYRIZI	75% (229/304)	75% (220/294)	88% (267/304)	84% (246/294)	36% (109/304)	51% (149/294)
PLACEBO	5% (5/102)	2% (2/98)	8% (8/102)	5% (5/98)	0% (0/102)	2% (2/98)

NRI=Non-Responder Imputation.

MAINTENANCE OF RESPONSE[1]

In the randomized trials, among patients who achieved PASI 90 or PASI 100 at Week 16:

- **88%** maintained PASI 90 at Week 52 (n=398/450; NRI)
- **80%** maintained PASI 100 at Week 52 (n=206/258; NRI)

STUDY DESIGN[2]

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

INDICATION[1]

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

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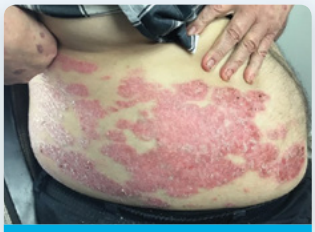
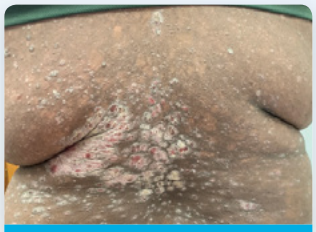
REAL PATIENTS. REAL RESULTS.

WEEK 0 (BASELINE)

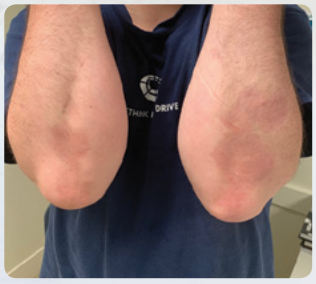
PATIENT FROM ILLINOIS

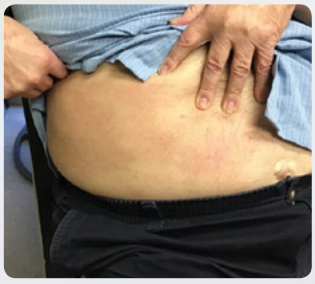


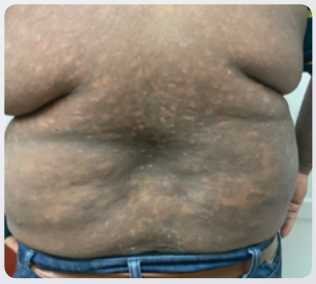
PATIENT FROM TEXAS



PATIENT FROM TENNESSEE







WEEK 16 (AFTER TWO DOSES)

Patient photos representing results captured at baseline and Week 16, outside of clinical trials.[3]

The patients depicted above have moderate to severe plaque psoriasis with an affected body surface area ≥10.[3]

Left: Photos courtesy of Dr. Meyer Horn. **Middle:** Photos courtesy of Matt Bruno, PA. **Right:** Photos courtesy of Dr. Ellen Frankel.[3]

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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 accompanying Brief Summary of Full Prescribing Information on the next page.

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661. **3.** Data on file, AbbVie Inc. Rep-fielded images. Presented: June 16, 2020.

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Skyrizi®
risankizumab-rzaa

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]*.

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ORIGINAL ARTICLE

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Tumescent Anesthesia: A Brief History Regarding the Evolution of Tumescent Solution

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ABSTRACT

Tumescent anesthesia, initially developed as a safer and more effective alternative to general anesthesia in performing liposuction, is used extensively today for a wide array of surgical procedures performed by various specialties. The make-up of the tumescent solution is variable, and it has evolved significantly over the past 40+ years. Even prior to Jefferey Klein's tumescent solution recorded in his article from 1987, "The Tumescent Technique for Lipo-Suction Surgery," there were significant contributions paving the way to modern formulations.[1] In this article, we attempt to provide the most comprehensive history and timeline documenting the evolution of tumescent solution to date.

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INTRODUCTION

The term tumescence, by definition, is the state of being swollen. When we speak of tumescent anesthesia, we broaden this to include swollen tissue with various amounts of analgesics and vasoconstrictive agents. The general concept is an old one. In fact, the idea that large volumes of fluid may be introduced into subcutaneous tissue in order to provide a degree of local analgesia was known as "massive infiltration" in the early part of the 20th century.[27] The addition of small amounts of analgesics, known as "massive infiltration analgesia with weak analgesic solutions," was being used in the United States by 1915.[27] Meanwhile in Russia, a surgeon named Aleksandr Vasilyevich Vishevsky was developing a similar technique that he published in 1932, which he called "Local Anesthesia by Creeping Infiltration Method," later known as the "Vishnevsky anesthetic technique."[28] However, these techniques were largely ignored in the surgical literature from the 1930's until the latter part of the 1970's, when they were first applied to liposuction. Since that time, the solutions used for infiltrating tissue have evolved considerably. In fact, from the late 1970's onward, it is difficult to document all of the significant changes and improvements that have occurred. In this brief history, we will attempt to highlight and discuss the major events, giving credit as appropriate, in the evolution of the tumescent solution. And it all started with liposuction.

DISCUSSION

Liposuction with hollow bore needles, under general anesthesia, was first reported by Giorgio Fischer in 1976.[3] This was performed without local infiltration of fluids or analgesics. It was Yves-Gerard Illouz (Figure 1) who pioneered the "wet technique" in 1977, which involved the injection of small amounts of hypotonic saline, hyaluronidase and epinephrine into the subcutaneous fat.[3] According to a recent conversation with Dr. Richard Glogau, who learned liposuction from Illouz in Paris in 1981, Illouz began using lidocaine with epinephrine in his solution at some point between 1977–1981. He was not, initially, using this for anesthesia, but for the vasoconstrictive effect of the epinephrine. His procedures during this period were all performed under general anesthesia. A significant benefit of the wet technique is improved hemostasis, leading to a relatively bloodless surgical site, thus decreasing the potential risk of hematoma, seroma and ecchymosis.[35] Also, the hypotonic solution leads to swelling of tissue and lipolysis of adipocytes, facilitating easy removal of fatty tissue with less tissue damage.[35] Later, in 1984, Stegman and Tromovitch documented a method for small areas of liposuction to be performed using local anesthesia only (no general anesthesia and/or systemic analgesia) in their textbook, "Cosmetic Dermatologic Surgery."[30] The combination of these two concepts, the wet technique and local-only anesthesia for liposuction, collided with Dr. Saul Asken's work (Figure 2) in the early-to-mid 1980's.[35] Asken was on the verge of performing

FIGURE 1. Contributions of Yves-Gerard Illouz.

Yves-Gerard Illouz – The Wet Technique[3]
• Dr. Illouz, along with Dr. Pierre Fournier, began practicing liposuction shortly after its introduction by Dr. Gorgio Fischer in the mid-1970's. Dr. Illouz developed the "wet technique" to reduce bleeding and facilitate fat removal. • The wet technique consisted of infiltrating the area to be treated with small amounts of hypotonic saline, epinephrine, +/- hyaluronidase, in various amounts. • Procedures were still performed under general anesthesia.

FIGURE 2. Contributions of Saul Asken.

Saul Asken – The Modified Wet Technique[35]
• Dr. Asken was on the verge of performing procedures using true tumescent anesthesia in the early-to-mid 1980's, just prior to Klein's article on the tumescent technique in 1987. He expanded on work done by Illouz and Fournier with his "modified wet technique." • Dr. Asken's solution, documented in 1986: 1000 mg lidocaine (50ml 2% lidocaine) Epinepherine 1:100,000 250ml normal saline +/- additional 250ml chilled saline (cryoanesthesia) • In addition to local anesthesia, patients were given IV sedation.

FIGURE 3. Contributions of Jeffrey Klein.

Jeffrey A. Klein – The Tumescent Technique[1]
• Dr. Klein was the first to demonstrate true tumescent anesthesia, without the use of general anesthesia, systemic analgesics or conscious sedation. • Klein's 0.1% tumescent solution, documented in 1987: 1 L normal saline 1000 mg lidocaine (100 ml 1% lidocaine) 1. mg epinephrine 12.5 ml of 8.4% sodium bicarbonate +/- 1 ml (10 mg) triamcinolone

his surgical procedures using tumescent anesthesia only, but since he was using conscious sedation, his procedures at that time were not considered "true" tumescent technique. The first to perform surgical procedures under tumescent anesthesia only was Klein (Figure 3) who demonstrated the "tumescent technique" at the Second World Congress of Liposuction Surgery in 1986.[37]

The tumescent technique was first described in the literature by Dr. Jeffrey A. Klein, then professor of dermatology at the University of California Irvine, in 1987.[1] He developed this technique to provide a safer and more effective method for liposuction. Prior to this, liposuction was most typically performed in an operating room under general anesthesia. The tumescent technique involves the infiltration of large volumes of fluids with dilute amounts of local anesthetic agents and epinephrine, all performed without general anesthesia or significant conscious sedation. In addition to hypotonic saline and local anesthetic, various amounts of hyaluronidase, epinephrine, sodium bicarbonate and triamcinolone have been combined. We have attempted to chronicle the evolution of the tumescent solution over time (Table 1).

The most significant trend we noted over time is a decrease in the overall percentage of local anesthetic per solution. Lidocaine has been the local anesthetic agent most often used. To adequately interpret these changes, a brief discussion of the safe dosage of lidocaine is warranted. While the risk of serious complications using tumescent anesthesia is extremely low, there is the potential for lidocaine toxicity.[5] The FDA-approved recommended safe dosage of lidocaine with epinephrine for local anesthesia is 7 mg/kg. However, the safe range of lidocaine for tumescent anesthesia appears to be much higher. The actual safe dosage of lidocaine during tumescent anesthesia is not universally agreed upon. Originally, Klein demonstrated the safety of using 35 mg/kg lidocaine dosing with the tumescent technique.[7] In 2006, the American Society for Dermatologic Surgery guidelines called for a maximum safe level of lidocaine during tumescent anesthesia of 55mg/kg.[39] More recently, Klein et al measured serum concentrations of lidocaine in 14 subjects, who underwent tumescent infiltrations with lidocaine doses ranging from 19.2 to 52 mg/kg. Based on the results, they recommend maximum safe doses of lidocaine during tumescent anesthesia of 45 mg/kg with liposuction and 28 mg/kg without liposuction. Liposuction appears to remove between 20-25% of the lidocaine before it is absorbed.[37,38] Due to the constriction of blood vessels and the redistribution of lidocaine to peripheral tissue with increased molecular bonding, the absorption of lidocaine into the blood is significantly delayed. Thus, the peak serum concentrations stay below the threshold for mild lidocaine toxicity (6ug/ml), despite the higher overall amount lidocaine in the tumescent solution.[37,38] With that said, the more dilute the solution, the larger the area that can be treated with less risk of lidocaine toxicity. In his 2009 JAAD article, Habbema (Figure 4) demonstrated the effectiveness of lidocaine concentrations of 500 mg/L (0.05%) in all areas of the body, and even down to 400 mg/L (0.04%) for most areas treated.[5] Lidocaine concentrations below these numbers will lead to inadequate analgesia unless systemic sedation and/or analgesia is added.

Concerning local anesthetics, lidocaine is not the only player. Other local anesthetics that have been studied include prilocaine, mepivacaine, bupivacaine, and ropivacaine.[40] Several countries in Europe, including Germany and Austria, have used prilocaine, either alone or in combination with lidocaine, in their solutions

FIGURE 4. Contributions of Louis Habbema.

Louis Habbema – Lowest Effective Anesthetic Concentration[5]
• Dr. Habbema has performed liposuction using tumescent anesthesia only since 1996. He started with a solution very similar to Klein's initial solution and gradually decreased the concentration of lidocaine. • In 2010, he published a significant article in the Journal of the American Academy of Dermatology evaluating 3430 cases of liposuction using tumescent anesthesia with variable concentrations of lidocaine. • He found effective anesthesia for all body parts with lidocaine diluted to 400 mg/L (0.04%) for most areas and 500 mg/L (0.05%) for sensitive areas. • Dr. Habbema's solution, as documented in 2010: 1 L normal saline 400-500 mg lidocaine 0.8-1.0 mg epinephrine 10.0 ml of 8.4% sodium bicarbonate

TABLE 1.

Timeline of Modern Tumescent Solution

Year	Author	Solution	Percentage of Anesthesia in Solution	Notes
1977	Y. Illouz[3*]	Small amount of hypotonic saline, with epinepherine +/- hyaluronidase, in various amounts. (Wet Technique)	NA	Patient was still under general anesthesia. The small amount of solution was used to create a relatively bloodless surgical site.
1984	T. Stegman, T. Tromovitch[30]	0.5% lidocaine, 1:200,000 epinephrine, plus hyaluronidase 1cc/30ml lidocaine. Up to 100ml as needed.	0.5% lidocaine	Small areas of fat done with local anestesia only. No tumescent solution yet.
1986	Asken[35]	1000 mg lidocaine (50ml 2% lidocaine,) epinepherine 1:100,000, 250ml NS, +/- additional 250ml chilled saline	0.4% lidocaine (0.2% with cryo-anesthesia solution)	Modified "wet technique," +/- cryoanesthesia which would reduce the overall percentage of lidocaine by up to 50%, plus consious sedation.
1987	Klein[1]	1 L normal saline, 1000mg lidocaine (100ml 1% lidocaine,) 1.0mg epinephrine, 12.5 ml of 8.4% sodium bicarbonate, +/- 1 ml (10mg) triamcinolone	0.1% lidocaine	Klein 1987
1989	Illouz[32]	1 L normal saline, 600mg lidocaine (60ml 1% lidocaine,) 1mg epinephrine.	0.06% lidocaine	The amount injected should be the same as the amount of fat to be removed. Most procedures (anything greater than 1000ml aspirate, were still done under general anesthesia as well.)
1990	Klein[29]	1 L normal saline, 500mg lidocaine (50 ml 1% lidocaine,) 1mg epinephrine (1ml of 1:1,000 solution of epinephrine,) 12.5 ml of 8.4% sodium bicarbonate	0.05% lidocaine	
1990	Stegman, Tromovitch, Glogau[31]	800ml normal saline, 480mg lidocaine (48ml 1% lidocaine,) 160ml sterile water, 0.8mg epinephrine (0.8ml of 1:1,000 solution of epinephrine,) hyaluronidase 800 I.U.	0.06% lidocaine	
1991	P. Fournier[33]	500ml chilled NS at 2 degrees C, 500mg lidocaine (50ml 1% lidocaine,) 1mg epinephrine	0.1% lidocaine	Syringe technique: Inject lidocaine with epinephrine first, approximately 2cc every 3cm. Wait 15 minutes, then infiltrate with chilled NS.
1994	Sattler[20]	1 L normal saline, 400mg Prilocaine, 1mg epinephrine, 6ml of 8.4% sodium bicarbonate, 1ml (10mg) triamcinolone.	0.04% prilocaine	Still used I.V. sedation and analgesia in some cases.
1996	Habbema[5]	1 L normal saline, 1000mg lidocaine (100ml 1% lidocaine,) 0.5-1.0mg epinephrine, 10ml of 8.4% sodium bicarbonate	0.1% lidocaine	
1998	Hamburger[20]	1 L normal saline, 200mg lidocaine (20 ml 1% lidocaine,) 200mg prilocaine, 1mg epinephrine, 6ml of 8.4% sodium bicarbonate, 1ml (10mg) triamcinolone.	0.02% lidocaine plus 0.02% prilocaine	Still used I.V. sedation and analgesia in some cases.
2005	Hanke, Sattler[3]	0.05% - 0.15% lidocaine. For the 0.05% solution: 1 L normal saline, 500mg lidocaine (25ml of 2% lidocaine,) 1mg epinephrine (1 ml of 1:1000 epinephrine,) 10ml of 8.4% sodium bicarbonate	0.05% lidocaine	
2008	Habbema[5]	1 L normal saline, 400-500mg lidocaine, 0.8-1.0mg epinephrine, 10ml of 8.4% sodium bicarbonate	0.04-0.05% lidocaine	
2016	Sandhofer[36]	3 L normal saline, 700mg lidocaine (35 ml 2% lidocaine,) 3 mg epinephrine, 45 ml of 8.4% sodium bicarbonate	0.0233% lidocaine	Plus I.V sedation and analgesia

Rows in beige represent solutions/procedures not to be considered true tumescent anesthesia. General anesthesia and/or systemic analgesics are involved.
Rows in white represents true tumescent anesthesia.
*Note: At some point between 1977-1981, Illouz began using lidocaine with epinepherine in his solution. He was not, initially, using this for anesthesia, but for the vasoconstrictive effect of the epinepherine. All of his procedures during this period were performed under general anesthesia. The dermatologists who visited Illouz in Paris in 1981-1982 observed him to be using lidocaine in the anesthesia mixture. Following Klein's publication in 1987, Illouz reduced the lidocaine concentrations in his anesthetic mixture to 0.06%. He continued to use general anesthesia primarily. Many dermatologists were performing non-tumescent liposuction using only local anesthesia for small aspirations in the early and mid 1980's.

TABLE 2.

Timeline with Corrected Concentration of Anesthetic			
Year	**Author**	**Percentage of Anesthesia in Solution (Reported in Liturature)**	**Percentage of Anesthesia in Solution (Calculated based on total volume)**
1977	Y. Illouz[3]	NA	NA
1984	T. Stegman, T. Tromovitch[30]	0.5% lidocaine	0.5% lidocaine
1986	Asken[35]	0.4% lidocaine (0.2% with cryoanesthesia solution)	0.33% lidocaine (0.18% with cryoanesthesia solution)
1987	Klein[1]	0.1% lidocaine	0.09% lidocaine
1989	Illouz[32]	0.06% lidocaine	0.057% lidocaine
1990	Klein[29]	0.05% lidocaine	0.047% lidocaine
1990	Stegman, Tromovitch, Glogau[31]	0.06% lidocaine	0.057% lidocaine
1991	P. Fournier[33]	0.1% lidocaine	0.09% lidocaine
1994	Sattler[20]	0.04% prilocaine	0.038% prilocaine
1996	Habbema[5]	0.1% lidocaine	0.09% lidocaine
1998	Hamburger[20]	0.02% lidocaine plus 0.02% prilocaine	0.019% lidocaine plus 0.019% prilocaine
2005	Hanke, Sattler[3]	0.05% lidocaine	0.048% lidocaine
2008	Habbema[5]	0.04-0.05% lidocaine	0.038-0.047% lidocaine
2016	Sandhofer[36]	0.0233% lidocaine	0.0228% lidocaine

Rows in beige represent solutions/procedures not to be considered true tumescent anesthesia. General anesthesia and/or systemic analgesics are involved.
Rows in white represents true tumescent anesthesia.

with good results.[43] Safety concerns over methemoglobinemia with prilocaine are real, but the risk is limited with combination solutions. Theoretically, larger amounts of total anesthetics should be safe with the combination of lidocaine and prilocaine.[44]

One additional factor that seems to have been overlooked in the literature concerns the way lidocaine is calculated in tumescent anesthesia solution. The lidocaine concentration is sometimes given as a percentage of lidocaine per L of normal saline. Other times it is given as an amount (mg of lidocaine) per L of normal saline. Based on our review of the literature, there appears to be an overestimate of the total amount of lidocaine in just about every case. The true calculation should be based on the total solution (which includes the amount of normal saline, but also needs to include the small amount of fluid in the lidocaine, sodium bicarbonate, epinephrine, etc.) Take, for example, Klein's solution from 1987: 1 L normal saline, 100ml of 1% lidocaine, 1ml epinephrine (1mg,) 12.5 ml of 8.4% sodium bicarbonate, +/- 1 ml (10mg) triamcinolone.[1] He initially calculated his overall percentage of lidocaine (0.1%) using 1000mg (100 ml) for the numerator and 1000 ml, the amount of normal saline, for the denominator. The true denominator should technically include the entire solution, which is 1113.5 ml (1000 ml normal saline, 100 ml 1% lidocaine, 12.5 ml sodium bicarbonate, 1 ml epinephrine.) This calculation gives the actual amount of lidocaine per total solution and changes Klein's original 0.1% lidocaine solution to 0.09%. In terms of the amount of lidocaine, instead of 1000 mg per L saline, the true number is closer to 900 mg per L of total solution. This is important in calculating the overall amount of lidocaine given during a procedure when using tumescent anesthesia. We have included an additional table that compares our adjusted percentage of anesthesia, based on these calculations, compared with the percentages reported in the literature (Table 2).

CONCLUSION

It is not possible to fully document every change that has led to modern tumescent anesthesia solutions. The likely fact is that many formulas evolved by trial and error, sometimes going undocumented in the literature, building upon the progress of others. The 1980's were an exciting time of new discoveries, mainly involving liposuction, that eventually resulted in true tumescent anesthesia with Klein's tumescent technique in 1987. Klein coined the term "tumescent technique" in 1987 to describe liposuction performed totally under tumescent local anesthesia only. The term "tumescent local anesthesia" first appeared in the German literature in 1999 and in the American literature in 2001.[21,42] Since Dr. Klein first pioneered the tumescent technique as applied to liposuction, tumescent anesthesia has since gained momentum in multiple specialties for various procedures. Dermatology, plastic surgery, vascular surgery, general surgery, and orthopedics have all applied the tumescent technique to procedures that were once only performed under general anesthesia. Some applications outside of dermatology include breast augmentation/reduction,[12,13] mastectomy,[14] face/neck lift,[15] abdominoplasty,[9] phlebectomy/venous stripping,[16] inguinal hernia repair,[11] hand surgery,[10] lymph node dissection[17] and scar repair/contracture release.[19] The applications will continue to

increase, given the significant benefits of tumescent anesthesia. In this brief history, we have attempted to document the major breakthroughs leading to the modern tumescent solution, highlighting contributions from those involved in the process. We believe this is the most comprehensive such history to date.

DISCLOSURES

The authors have no conflict of interest.

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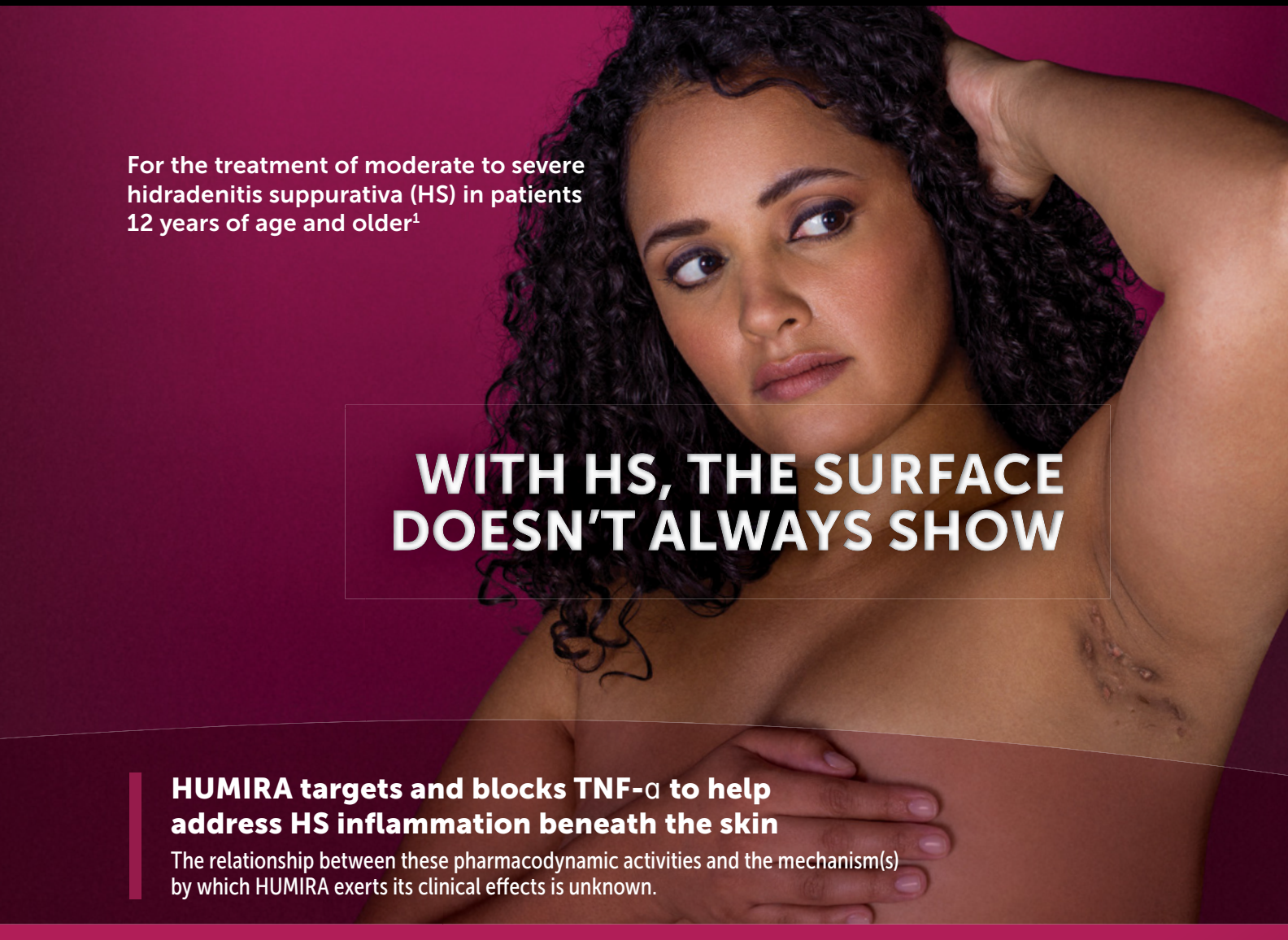


For the treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older[1]

WITH HS, THE SURFACE DOESN'T ALWAYS SHOW

HUMIRA targets and blocks TNF-α to help address HS inflammation beneath the skin

The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

HUMIRA delivers clinically meaningful improvement (HiSCR) at week 12[1,3]

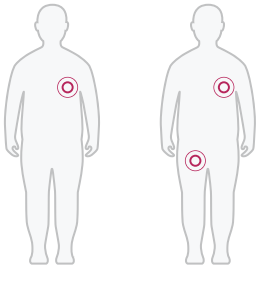
In the PIONEER clinical trials, **42%** (PIONEER I) and **59%** (PIONEER II) of HUMIRA-treated adult patients achieved HiSCR* at Week 12 **(primary endpoint)**, vs 26% and 28% on placebo, respectively.[3]

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.**[3]

*HiSCR=Hidradenitis Suppurativa Clinical Response.

LESION SPREAD:

Lesion observed in any anatomic region not seen at baseline[4]



Baseline | Example of lesion spread

◎ Lesions=abscesses, inflammatory nodules, or draining fistulas[4]

HUMIRA has data on lesion spread for HS

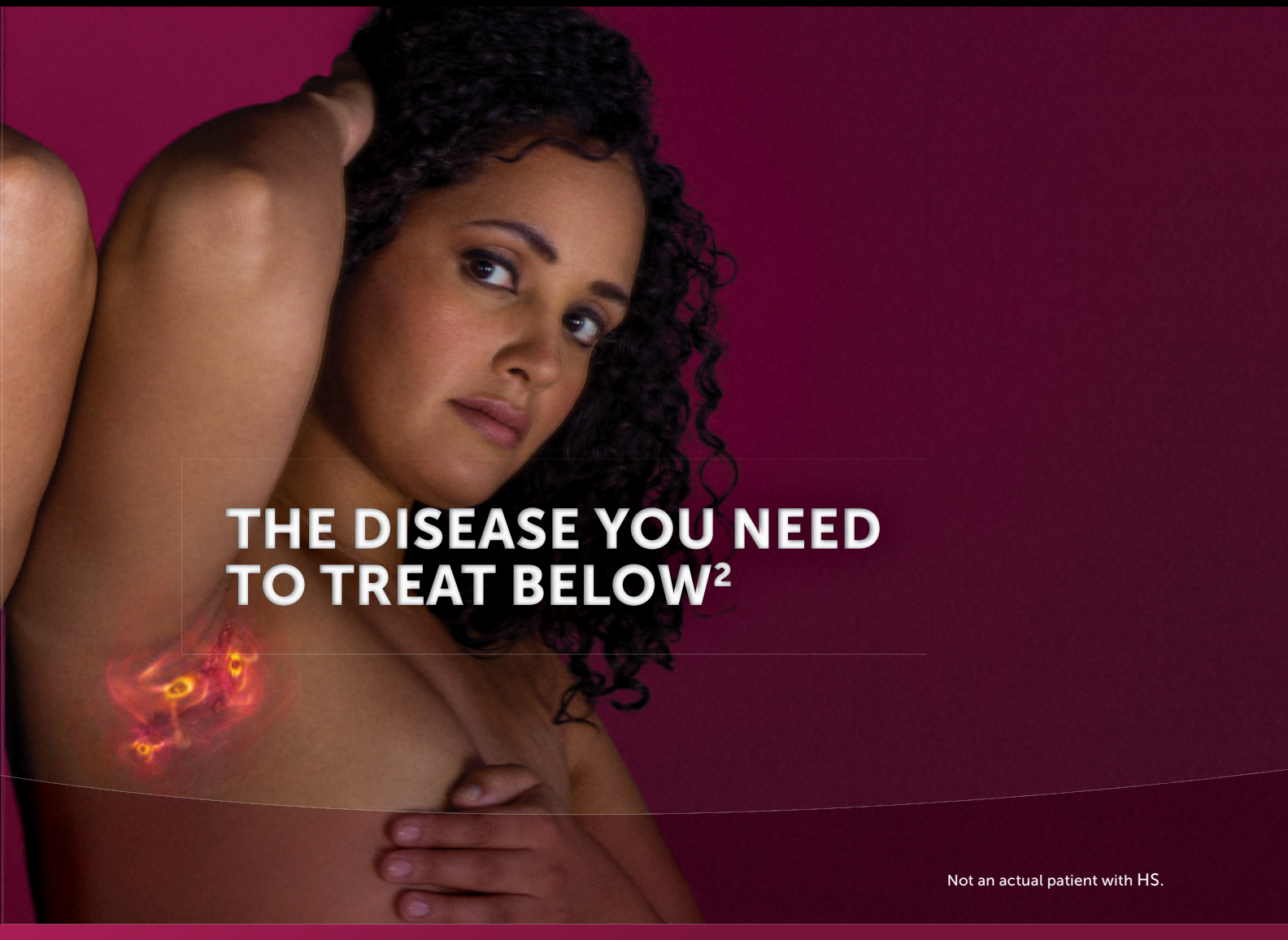
In a post-hoc analysis, **47%** of HUMIRA-treated adult patients (n=99, PIONEER I/II) did not experience lesion spread at week 36 vs **25%** in control group (n=151, PIONEER II)[4]

DATA LIMITATIONS:

- **Lesion spread was not a pre-specified endpoint and was not controlled for multiplicity. This data cannot be regarded as statistically or clinically significant, and therefore, no conclusions can be drawn.**
- **Placebo comparator data are only available from PIONEER II so differences should be interpreted with caution.**

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

PRIMARY ENDPOINT HiSCR at week 12 (Period A), defined as ≥50% reduction from baseline in abscess and inflammatory nodule count, with no increase in abscess and draining-fistula count.[1,3] In an integrated exploratory post-hoc analysis of PIONEER I and II, lesion spread was assessed through 36 weeks in patients randomized to HUMIRA 40 mg weekly or placebo in Period A and B.[4]



To learn about dosing: HUMIRADERMPRO.COM/HS/dosing

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.**

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.

HUMIRA® adalimumab

IMPORTANT SAFETY INFORMATION[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.** Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. 2019;80(1):60-69.e2. doi:10.1016/j.jaad.2018.05.040 **3.** 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. doi:10.1056/NEJMoa1504370 **4.** Data on file. ABVRRTI71291.

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

HUMIRA® adalimumab

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]*.

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ORIGINAL ARTICLE

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A Patient-Centered Guide to Hidradenitis Suppurativa Flare Prevention

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic debilitating skin disease characterized by painful dermal abscesses, subcutaneous inflammatory nodules, draining sinuses and hypertrophic scars. Prompt recognition and management of the disease is of the utmost importance as prolonged disease can have long-standing physical and psychological consequences. Quality of life and symptom improvement are viable outcomes from preventative interventions in patients with HS. While there is not a cure for HS, symptoms can be managed, and recurrence can be reduced following various lifestyle changes. Treatment should be focused on prevention of disease progression, reducing the frequency of recurrence, and treating existing lesions to minimize pain and drainage.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that predominantly affects young adult females in the second and third decades of life.[1] Clinically, HS is characterized by painful dermal abscesses, subcutaneous inflammatory nodules, draining sinuses, and hypertrophic scars involving the axillae, anogenital region, breast, areola, and periumbilical region.[2] HS can be associated with malodorous discharge and significant disfigurement, which may have a large impact on the patients' quality of life.[3]

The pathogenesis of HS is not fully elucidated; however, lesion formation is believed to be centered around follicular occlusion within apocrine glands resulting in debris accumulation, leading to cyst formation. Eventually, the hair follicle will rupture, followed by a local immune response resulting in substantial inflammation.[4] In advanced cases, the sinuses in HS can dissect into fascia and muscle, forming tracts.[2] Genetic factors, immune dysregulation, hormonal imbalance, and lifestyle influence also play a role in the development of HS.[5] Common associated comorbidities include obesity; as well as HTN, metabolic syndrome, depression, diabetes mellitus, Crohn's disease, and cardiovascular disease. Additionally, there is a strong association between smoking and HS.[1]

Historically, HS has been treated by a number of different specialties including surgeons, emergency physicians, infectious disease specialists, general practitioners, and dermatologists. The lack of cohesive care has led to variations in the approach to the signs and symptoms of HS, as well as disease management. This fragmentation in care may lead to a delay in diagnosis of HS, reported to range from 5-14 years.[6] Early lesions of HS mimic other skin conditions and are often misdiagnosed as recurrent furunculosis, or folliculitis.[7,8] Rapid recognition and initiation of treatment can reduce the risk of HS progression to debilitating end-stage disease, which involves the diffuse development of sinus tracts and abscesses across an entire body surface.[7,9] It is imperative that HS be promptly diagnosed and managed to avoid long-term consequences such as depression, anxiety, and scarring which can be associated with mismanaged HS.[10]

Practical Interventions

HS is a complex disease that requires a patient-centered approach, including management of the disease, its comorbidities, and flare prevention.[5] While there is not a cure for HS, symptoms can be managed and recurrence can be reduced following various lifestyle changes.[11] Common goals of management include prevention of disease progression, reducing the frequency of recurrence, and treating existing lesions to minimize pain and drainage.[12]

Weight Loss

The link between HS and obesity is rooted in obesity's inflammatory nature, which creates a milieu of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha – all of which mediate inflammation seen in HS. Furthermore, having increased inverse skin areas in the axilla and inguinal folds poses opportunity for localized friction leading to follicular hyperkeratinization and occlusion.[13]

TABLE 1.

Practical Interventions for the HS Patient	
Intervention	**Details**
Weight Management	• Diet - Restrict calories by 500–1000 kcal/day (should be individualized and based upon current BMI) • Exercise - 30–60 minutes of aerobic exercise 3–5 days/week
Nutrition	• Vitamin D - Consider vitamin D supplementation in patients who are deficient. • Vitamin B12 - Consider vitamin B12 injections in patients with deficiencies. • Zinc - Consider zinc supplementation in patients with and without zinc deficiency. • Mediterranean Diet - Consider a diet high in olive oil, leafy green vegetables, fruits, nuts, legumes, as well as a moderate intake of fish, meat, and red wine. • Dairy Avoidance • Yeast Avoidance - Avoid yeast-containing foods such as bakery products, vinegar, black tea, soy sauce, beer, wine, and fermented cheese
Clothing Considerations	• Avoid tight-fitting clothing over inflamed areas of the skin. • Choose clothing items containing cotton, linen, or merino wool to allow for more breathability.
Hygiene Practices	• Applying a warm compress can alleviate pain and reduce inflammation. • Consider antibacterial washes, weekly diluted bleach baths (under the guidance of a physician), and keeping affected areas clean and dry.
Grooming Practices	• Avoid shaving with a razor to prevent worsening inflammation.
Smoking Cessation	• Counseling • Medications (under the guidance of a physician) - Varenicline - Bupropion
Pharmacologic Options	• Clindamycin 1% twice daily until flare improves • 100 mg twice daily of doxycycline or minocycline for 3 months • Isotretinoin (0.45/mg/kg/day) • Biologic anti-TNF agents can be considered in severe disease
Surgical Interventions	• Incision & drainage • CO_2 laser excision

Due to the linkage between obesity and HS, HS patients are advised to maintain a healthy body weight. For weight loss, restricting calories by 500–1000 kcal/day is ideal.[14] The Academy of Nutrition and Dietetics does not recommend a specific diet for weight loss, but restrictive diets such as low-carbohydrate or a high fiber diet can be beneficial for creating energy deficits necessary for weight loss.[15] Measures can be taken to make exercise more comfortable for patients with active HS lesions. Low impact exercise, such as swimming, yoga, or Pilates, can help boost patient comfort. Exercise plans can be modified to accommodate for active lesions. For example, if a patient is experiencing active underarm lesions, a lower body exercise routine could be completed or vice versa.[16] Exercise, combined with diet, can encourage weight loss and overall health, which will lead to a decrease in inflammatory markers, less friction in skin folds, and overall improvement of HS flares.

Dietary Considerations

The role of diet in HS is not well understood; however, there are several nutritional interventions patients can take to reduce disease severity. Supplementation can include vitamin D, vitamin B12, and zinc. Avoiding certain foods such as brewer's yeast and dairy can also be of benefit. In addition, adhering to a Mediterranean diet can have positive effects on disease severity. Referring patients to a nutritionist to assist with formulating a diet plan can be beneficial.

Vitamin D

Patients with HS have abnormal keratinocyte proliferation and hair growth cycles, as well as immunologic dysfunction. As a result, patients are susceptible to colonization and infection with pathogenic bacteria. Vitamin D supplementation decreases secondary infections by increasing the synthesis

of antimicrobial peptides and normalizing keratinocyte proliferation.[17] A prospective study by Guillet et al determined that of the 22 patients included in this study with HS, 100% of them were deficient in vitamin D. With high dose supplementation, 79% of patients showed a 20% reduction in flare frequency and number of nodules ($P< 0.05$).[18] In HS patients who are vitamin D deficient, it is recommended to supplement with vitamin D3, 100,000–600,000 IUs, depending on the severity of the deficiency.[18] It should be noted that this link is not well established and further investigation is needed to determine an appropriate dosing regimen.[18]

Vitamin B12

Vitamin B12 is essential for DNA synthesis, amino acid and fatty acid metabolism, as well as immune function. Three cases reported by Mortimore and Florin demonstrate that HS patients with concomitant inflammatory bowel disease (IBD) had complete resolution of HS when treated with vitamin B12 injection, however, statistical significance cannot be drawn.[19] In patients diagnosed with both IBD and HS, there could be potential benefit from monthly high-dose 1000 µg vitamin B12 intramuscular injections.[19]

Zinc

Zinc is believed to strengthen the immune system, decrease inflammation, and scavenge free radicals.[17] A qualitative pilot study of 22 patients with HS by Brocard et al. determined that supplementation with 90 mg of zinc gluconate daily led to complete remission in 8 patients and partial remission in 14 patients.[20] It was postulated that zinc supplementation plays a suppressive, rather than a curative role in the pathogenesis of HS.[20] Supplementation with 90 mg of zinc gluconate per day should be considered in patients with HS; however, statistical significance cannot be drawn from this specific study.[20] The link between zinc and the pathogenesis of HS is not well understood and further investigation is needed in order to fully determine its role.

Mediterranean Diet

The Mediterranean diet consists of a high intake of foods containing olive oil, leafy green vegetables, fruits, nuts, legumes, and a moderate intake of fish, meat, and red wine.[21] Following a Mediterranean diet that is high in antioxidants and polyphenols decreases the severity of HS through its anti-inflammatory effects. The anti-inflammatory potential of the Mediterranean diet is based on oxidized low-density lipoprotein (LDL) levels, a marker of oxidative stress involved with chronic inflammation. In a case-control study by Barrea et al (n=82), HS patients with a low oxidized-LDL level negatively correlated with adherence to the Mediterranean diet and positively correlated with disease severity ($P<0.05$).[22] As such, a Mediterranean diet should be recommended

Dairy Avoidance

It is postulated that dietary dairy can lead to obstruction of the follicular duct via androgen receptor mediation. Androgen receptors become available for ligand binding via increases in IGF-1 from both casein and insulin spikes due to whey and simple carbohydrates found in dairy products. Thus, androgen binding leads to filling of the folliculopilosebaceous unit with lamellar, poorly differentiated keratinocytes, resulting in obstruction.[23] A study by Danby et al (n=47) determined that 83% of patients reported improved pain, discharge, and odor on a dairy-free diet. As such, HS patients should aim to limit or eliminate dairy products in their diet.[23]

Yeast Avoidance

Anti-saccharomyces antibodies have long been associated with inflammatory diseases such as Crohn's disease (CD).[24] A case-control study by Egeberg et al determined that individuals with HS are at an increased risk for developing new-onset CD compared to healthy controls ($P<0.0001$).[25] Increasing evidence suggests that alterations in the gut microbiome, as evidenced by the presence of anti-saccharomyces antibodies, can influence the development of certain inflammatory diseases.[24] A prospective study by Aboud et al (n=185) determined that of the patients with HS following a yeast-exclusion diet, 70% reported an improvement in HS symptomatology without any other intervention.[26] A separate multicentric cross-sectional study by Assan et al. (n=148 HS patients) detected anti-saccharomyces cerevisiae antibodies in 24.3% of patients with HS ($P< 0.001$).[24] Present data supports the need for further investigation of the gut microbiome in the pathogenesis of HS; however, given the results from these two studies, patients should consider limiting yeast-containing foods, such as bakery products, vinegar, black tea, soy sauce, beer, wine, and fermented cheese.[26]

Clothing Considerations

Mechanical stress, such as friction, can lead to follicular occlusion and rupture. This stress is sensed by mechanotransducers in the skin, which can lead to activation of a pro-inflammatory cascade in keratinocytes and fibroblasts, resulting in local skin irritation. As such, friction should be minimized in the affected areas.[4] Patients should be counseled to avoid tight-fitting underwear, jeans, belts, bras, and collars, particularly over inflamed areas of the skin.[17] In addition to loose clothing, natural fibers such as cotton, linen, or merino wool are preferred as these materials will allow greater breathability. Synthetic materials like polyester, acrylic, and rayon should be avoided. Frequently changing clothing articles can prevent saturation due to discharge from the affected areas and is recommended for patients to both prevent an exacerbation of symptoms and to increase comfort during flares.[27]

Grooming Practices

There are conflicting reports on whether or not shaving plays

a role in the development of HS. Some studies report that shaving is associated with an earlier onset of disease, while others report that there is no negative impact of shaving on the development of HS.[10,28] Although the effects of shaving on the pathogenesis of HS are unclear, it should be recommended that patients avoid shaving the affected area, especially during an active flare. Shaving is considered a form of mechanical stress that can lead to worsening skin inflammation. Poor shaving techniques and shaving over uneven skin can lead to cuts and breaks in the skin that can act as a nidus for infections.[29]

Hygiene Practices

Due to the inflammatory nature of HS, warm baths can improve symptoms and provide comfort, while also reducing inflammation.[30] The majority of patients who bathe in warm water or apply warm compresses to the affected areas report immediate relief from pain and itching. The effectiveness of warm water in reducing pain and inflammation is thought to be secondary to the vasodilatory effects of warmer temperatures, leading to increased blood flow to the affected regions.[31] It is recommended that HS patients use warm baths or warm compresses for 10 minute intervals when pain is present in the disease process.[31] Very hot and cold water should be avoided as these can lead to dryness, irritation, and impairment of the epidermal barrier.[32]

Patients with HS are at increased risk for secondary bacterial infections due to bacterial colonization[2] therefore local hygiene and the use of antiseptics/topical antibiotics is an important practice.[33] One prospective study of 627 patients evaluated the efficacy of a three times daily antibacterial wash followed by a warm compress for 10 minutes, and the application of topical sodium fusidate 2% ointment. Complete healing of skin lesions was reported in over half of the patients by week two.[31] Dilute bleach baths 2–3 times weekly have also shown to be effective.[17] The use of antibacterial washes differ among clinicians and as such, further studies are necessary to elucidate their effectiveness. It should be noted, however, that while local hygiene can prevent secondary infection and improve wound healing, poor hygiene is not a direct cause of HS.[7]

Smoking Cessation

Tobacco use among patients with HS is exceedingly common with an estimated prevalence of 70–90%.[5] There have been several theories as to the role of cigarette smoking in the pathogenesis of HS, most agreeing that smoking acts as a proinflammatory stimulus or follicular occlusion promotor.[14] Chemicals such as nicotine, polyaromatic hydrocarbons, and dioxin-like compounds found in tobacco smoke activate keratinocytes leading to acanthosis, infundibular epithelial hyperplasia, and excessive cornification, all of which contribute to follicular occlusion.[4] Tobacco smoke also induces the expression of pro-inflammatory cytokines, thus contributing to the inflammatory nature of the disease.34 A causal relationship between smoking and HS has not yet been established; however, cessation is still recommended as it appears to reduce the severity and increase the remission of the disease.[5] To assist patients with smoking cessation, a combination of counseling, nicotine supplements, and medications (eg, varenicline and bupropion) is more effective than either approach alone.[14,35]

Wound Care

Because the skin barrier is disrupted in HS patients, properly managing wounds is critical. For a painful wound, a silver impregnated foam dressing is the preferred wound dressing due to comfortability, antimicrobial activity, ease of use, barrier management, and odor control.[14] Appropriately dressing and caring for wounds can lead to improved healing time.

Psychosocial Impact of HS Flares

Given the characteristic disfiguration and recurrent nature of the disease, HS undeniably has a profound impact on one's quality of life. The National Comorbidity Survey found an increased incidence of depression in HS patients of 20.2% when compared to the general population and patients with other dermatologic conditions.[36] Additionally, a study by Kouris et al showed a significant increase in anxiety of HS patients (P<0.001).[37] Painful flare ups can cause patients to avoid social situations due to malodorous abscess secretions or unsightly wounds or scars, which may lead to a negative body image. Furthermore, Alavi et al (n=100) found that males experienced greater rates of erectile dysfunction and women had a higher incidence of sexual distress compared to controls.[38] These social factors can have significant effects on patient quality of life. Current recommendations for addressing the psychosocial complications of HS include a multidisciplinary approach consisting of pharmacological and behavioral cognitive therapy, as necessary.[36] Treatment of depression and/or anxiety can help improve HS treatment compliance and subsequently lead to an increase in quality of life.[36]

Traditional Treatment

While the above measures can be taken to prevent flares and/or worsening of HS, traditional medical therapies remain the mainstay of HS treatment. These include pharmacologic interventions, surgical procedures, as well as laser therapy.

Pharmacologic Options

For a new flare, using topical clindamycin 1% lotion twice daily for 1 week, or until the flare improves, is currently recommended. If flares cannot be controlled with topical clindamycin, systemic antibiotics may be considered. Doxycycline or minocycline 100 mg twice daily for 3 months is the first line option for systemic antibiotic therapy. In severe HS, biologic anti-TNF agents can be considered. The use of retinoids for HS patients has yielded mixed results. In a retrospective chart review by Huang et al.

(n=25), approximately 33% of patients had complete response to isotretinoin therapy (0.45/mg/kg/day), 33% had a partial response, and the remaining third had no response (P=0.04).[39] Given these results, isotretinoin therapy can be considered as another treatment option.[39]

Surgical Interventions

The most common procedure for HS care is an incision and drainage (I&D).[11] If an HS lesion is persistent despite medical treatments and I&D, a wide excision can be completed. It should be noted, however, that this procedure has a high rate of recurrence.[11] CO_2 laser excision can be used for surgical removal of HS abscesses and nodules and may be associated with a lower risk of infection and postoperative complications.[40]

CONCLUSION

HS is a chronic and debilitating disease predominantly caused by follicular occlusion and subsequent inflammation. Prompt recognition and management of the disease is of the utmost importance as prolonged disease can have long-standing physical and psychological consequences. Quality of life and symptom improvement are viable outcomes from preventative interventions in patients with HS. It is important to note that while lifestyle modifications (such as weight loss and smoking cessation) have been shown to improve symptoms, they do not cure HS.[14] Use of both medical and surgical treatment options should be considered, as appropriate, to manage active lesions and outbreaks, however the psychosocial aspects of HS are best managed through preventative measures. The combination of weight management, smoking cessation, and limitation of inflammation can lead to less frequent and severe flares, thus allowing patients with HS to have an improved quality of life. Preventing outbreaks can be the cornerstone to disease management and should be a vital component of treatment plans to best serve patients.

DISCLOSURES

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

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Evaluation of Picosecond 755-nm Alexandrite Laser With a Diffractive Lens Array on Pore Size Reduction

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ABSTRACT

Objectives: Medications, lasers, and light therapy have all been shown to transiently minimize pore size. Current research of the 755-nm Alexandrite picosecond laser (Cynosure, MA) on pore size shows differing results regarding the efficacy, with one study of Asian volunteers (Fitzpatrick skin type IV) reporting "marked" improvement of pores, yet another study reporting no significant improvement in pore size in Chinese patients (Fitzpatrick skin type III–IV), causing some contention. This study aims to rectify the discordant results through the examination of the 755-nm Alexandrite picosecond laser on pore size reduction in a sample consisting of Fitzpatrick skin type I–III.

Methods: Patients who received 755-nm Alexandrite picosecond laser treatment for photorejuvenation, (6 mm lens array) with a fluence of 0.71 J/cm^2 of the face or head, with at least two treatments over four-week intervals were included in the study. A precision subject imaging system (Canfield VISIA® Complexion Analysis Generation 7, NJ) was used to assess three parameters of pore size (feature count, score, percentile rank) at each time period at right lateral, left lateral and frontal views. A Wilcoxin signed rank test was performed to compare differences between time periods and a mixed model ANOVA was utilized to account for patients who received less than three treatments. Significance level set to P=<0.05.

Results: 32 participants met criteria and underwent at least two picosecond laser treatments for photorejuvenation. There was an overall reduction in pore count in approximately 57% of participant data points from times 1 to 2 and 50% reduction from times 2 to 3. There was a 100% pore count reduction observed from baseline compared with the follow-up visit four weeks after the third treatment, at time 4. Further, there was a significant improvement of pores demonstrated by score from times 1 to 3 (Z= -2.197, P=0.028) as well as percentile rank between times 1 and 2 (Z= -2.070, P=0.038) and times 1 and 3 (Z= -2.201, P=0.028).

Conclusion: Future studies should investigate the longterm effect of 755-nm Alexandrite picosecond laser on pore size reduction as continued patient recruitment and data collection is necessary to effectively discern the 755-nm Alexandrite picosecond laser debate. Thus, prolonged follow up post treatment should be evaluated in order to determine if results are maintained. Nonetheless, the 755-nm Alexandrite picosecond laser shows promising results for the improvement of skin pores thus far.

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INTRODUCTION

Skin "pores" (SP) are visible topographic depressions at the tegument surface that correspond to the ostia of pilosebaceous follicles or eccrine sweat glands. They are most commonly located on the face.[1] The term "pore" is a misnomer as these funnel-shaped cutaneous depressions may macroscopically appear as apertures, but they are not true orifices.[1] SP are benign and physiologically present in all individuals but may become a cosmetic concern when perceived as enlarged. Both endogenous and exogenous factors such as sex, genetic predisposition, aging, hormonal factors, chronic ultraviolet exposure, comedogenic xenobiotics, acne and seborrhea are known causes of pilosebaceous pore enlargement.[2,3]

Treatment modalities ranging from medications (eg, tazarotene cream, isotretinoin, glycolic acid peeling), light therapy (eg, intense pulse light) and lasers (eg, Nd:YAG, Clear + Brilliant® fractionated) have all been shown to transiently minimize pore size.[4-7] In 2012, the first picosecond laser (PicoSure®, Cynosure, Westford, MA) was FDA cleared for the treatment of unwanted tattoos/pigmented lesions.[8] The picosecond laser's pulse duration of 1/1000th of a nanosecond effectively generates more photomechanical than photothermal effects and simultaneously minimizes collateral thermal damage.[9] The diffractive lens array (DLA) was developed to effectively deliver intensified picosecond energy in a fractionated manner while maintaining a high safety profile through low total fluence.[10] The diffractive lens comprises individual lenses organized in an array with 500-um center-to-center spacing, which enables the redistribution of energy into high-fluence microbeams at a fixed spot size.[11] When used in conjunction with the picosecond Alexandrite laser, 70% of the energy is delivered into these high-energy zones while the residual energy is distributed over a low fluence background.[11]

Since its inception, the 755-nm Alexandrite picosecond laser has not only proved to be safe in skin of color, but has been used for a myriad of cutaneous conditions including acne scars, striae, wrinkles and pores.[12] Visual improvement in pore size has been subjectively observed with the use of the 755-nm Alexandrite picosecond laser (PicoSure®; Cynosure, MA).[11,13] However, current research is contradictory, with one study of twenty Asian volunteers (Fitzpatrick skin type IV) reporting "marked" improvement of pores after three treatments,[14] yet another study reporting no significant improvement in pore size in eighteen Chinese patients (Fitzpatrick skin type III–IV) after six sessions,[15] resulting in conflicted conclusions. This study aims to rectify the discordant results through the examination of the 755-nm Alexandrite picosecond laser (PicoSure®) with a diffractive lens array (DLA) on pore size reduction in a sample consisting of Fitzpatrick skin type I-III.

MATERIALS AND METHODS

This retrospective analysis was conducted at a single dermatology center. Thirty-two (*N*=32) American female subjects, ages 28 to 60 (mean age, 48 years old) with Fitzpatrick skin type I–III consented to photorejuvenation treatment. Patient demographics are summarized in Table 1. Those who received at least two treatments over four-week intervals met the inclusion criteria. Patients who received other concomitant treatments such as laser, light or topical eg, CO2 ablative, fractional resurfacing, Nd:YAG, intense pulsed light, tazarotene cream, isotretinoin, or glycolic acid peeling were excluded from final analysis.

Intervention

A 755-nm wavelength, 750-pulse duration Alexandrite picosecond laser (PicoSure®; Cynosure, MA) with a 6 mm lens array, pulse fluence of 0.71 J/cm^2 and 10 Hz repetition rate was used to treat the entire face. The treatment area was prepped and cleaned prior to the procedure. Topical anesthesia was achieved with the application of ointment (Benzo 20%, Lido 8%, Tetra 4%) 30 minutes prior to procedure. The target area received a range of 5000–13660 pulses in order to achieve the clinical endpoint of mild to moderate erythema based on treating physician's discretion. Forced cooled air was applied during the treatment and a cooling pad was applied post procedure. Patients were provided with post care instructions.

Objective assessments were conducted at baseline and every 4 weeks at each follow-up visit. A precision complexion analysis imaging system (VISA® Generation 7, Canfield Scientific, Parsippany, NJ) was used to assess three parameters of pore size (feature count, score, percentile rank) at each time period at right lateral, left lateral and frontal views, which were taken from a fixed angle, flash and distance. Photographs were taken under standardized lighting.

Statistical Analysis

Data analysis was conducted via SPSS v26 (SPSS Inc, Chicago, IL). The Wilcoxin signed rank test was performed to compare differences between time periods and a mixed model ANOVA was utilized to account for patients who received less than three treatments. Significance level set to P=<0.05.

TABLE 1.

Patient Demographics	
	Number of Respondents (%)
Age (years)	
21-30	1 (3.12)
31-40	5 (15.63)
41-50	14 (43.75)
51-60	11 (34.38)
>60	1 (3.12)
Female, *N*	32 (100)

RESULTS

VISA scores (feature count, score, percentile rank) from each time period were calculated and grouped chronologically for comparison (Figures 1-4), and subsequently transferred into SPSS for further analysis. The feature count provides the discrete number of pores detected within the mask area and the absolute score represents the total size, area and intensity of the pores, with lower scores indicating better pore quality.[16] While the percentile rank is generated based on the age and skin type with a higher score indicating better pore quality. After conducting the mixed model ANOVA, we found no significant difference between the time points. Though there was an overall reduction in pore count (measured in front and right and left lateral views) in approximately 57% of participant data points from times 1 to 2 and 50% reduction from times 2 to 3, it was not at the significant alpha level. VISA pore analysis for each time period is summarized in Tables 2a and 2b.

FIGURE 1. Pores. (A) Time 1 (B) Time 2. There is a decrease in feature count from time 1 (182) to 2 (257) and an improvement in score from 15.028 to 9.745. The patient ranked 26% at time 1 to 79% at time 2.

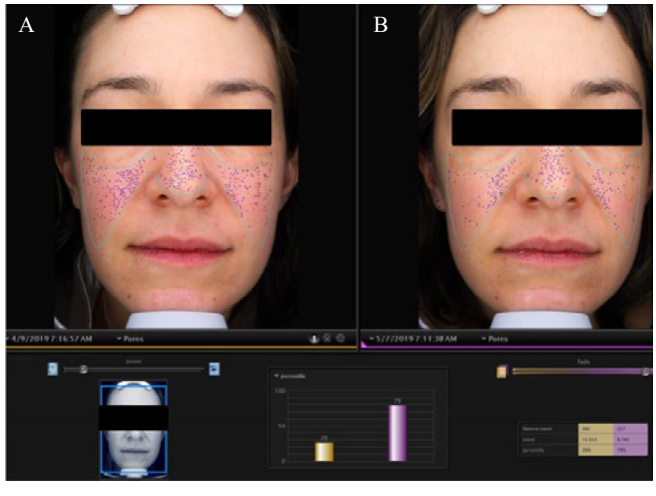


FIGURE 2. Pores. (A) Time 1 (B) Time 2. There is a decrease in feature count from time 1 (256) to 2 (233) and an improvement in score from 8.395 to 7.627. The patient ranked 9% at time 1 to 90% at time 2.

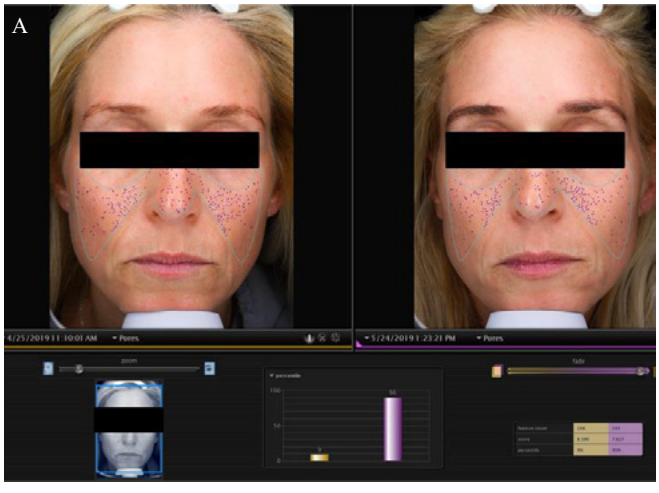


FIGURE 3. Pores. (A) Time 1 (B) Time 2. There is a decrease in feature count from time 1 (610) to 2 (292) and an improvement in score from 21.496 to 11.071. The patient ranked 9% at time 1 to 59% at time 2.

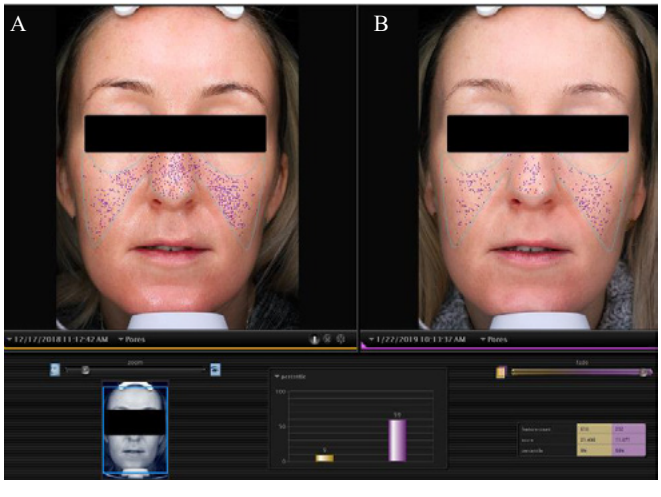


TABLE 2A.

VISIA Pore Analysis Before and After Picosecond Laser Treatment (Time 1 vs Time 2)			
	Before	After	p^*
Score			
Front	9.642 ± 4.192	8.9056 ± 3.908	.096
Left Lateral	9.681 ± 5.583	9.0159 ± 4.584	.489
Right Lateral	9.762 ± 3.942	9.4919 ± 4.249	.369
Percentile Rank (%)			
Front	67.500 ± 29.835	77.094 ± 22.582	.038
Left Lateral	69.406 ± 30.629	76.094 ± 24.227	.393
Right Lateral	64.688 ± 30.144	72.125 ± 25.233	.214
Count			
Front	362.031 ± 229.512	351.125 ± 206.899	.364
Left Lateral	326.186 ± 163.061	297.813 ± 161.763	.347
Right Lateral	333.000 ± 125.967	331.594 ± 153.509	.758

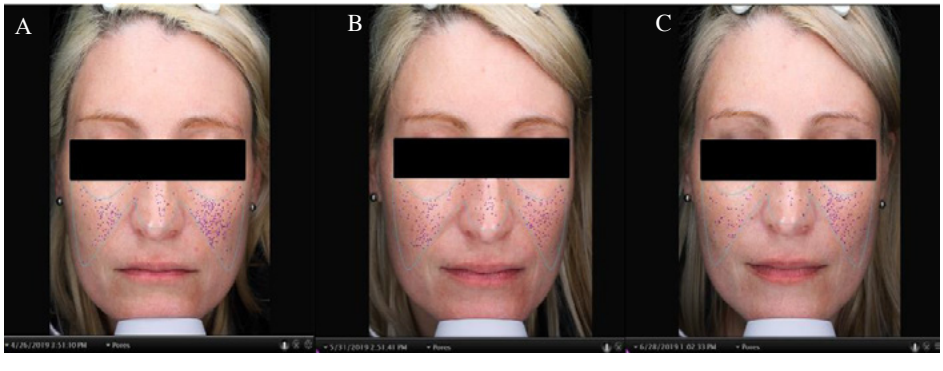
Data are expressed as mean ± SD.
$^*p < 0.05$ indicated significant difference.

TABLE 2B.

VISIA Pore Analysis Before and After Picosecond Laser Treatment (Time 1 vs Time 3)			
	Before	After	p^*
Score			
Front	9.642 ± 4.192	7.2466 ± 4.489	.398
Left Lateral	9.681 ± 5.583	6.7634 ± 2.795	.237
Right Lateral	9.762 ± 3.942	6.1600 ± 3.295	.028
Percentile Rank (%)			
Front	67.500 ± 29.835	82.286 ± 26.088	.116
Left Lateral	69.406 ± 30.629	88.571 ± 10.829	.075
Right Lateral	64.688 ± 30.144	88.143 ± 16.926	.028
Count			
Front	362.031 ± 229.512	249.714 ± 137.159	.128
Left Lateral	326.186 ± 163.061	251.714 ± 104.807	.237
Right Lateral	333.000 ± 125.967	223.000 ± 118.729	.176

Data are expressed as mean ± SD.
$^*p < 0.05$ indicated significant difference.

FIGURE 4. Pores. (A) Time 1 (B) Time 2 (C) Time 3. There is consistent decrease in feature count from time 1 (284) to 2 (245) and 3 (197). Score improves from 13.025 to 9.789 to 7.854. The patient ranked 9% at time 1, 78% at time 2, and 88% at time 3.



In addition, there was a 100% reduction observed from baseline compared with the follow-up visit at time 4, but this was in a sample of n=1. Since a small sample size can impact normal distribution[11], a Wilcoxin signed rank test was subsequently performed to compare differences between time periods, which showed a significant improvement of pores demonstrated by score from times 1 to 3 (Z= -2.197, *P*= 0.028) as well as percentile rank between times 1 and 2 (Z= -2.070, *P* = 0.038) and times 1 and 3 (Z= -2.201, *P*= 0.028). Post laser adverse effects of erythema, edema, pinpoint bleeding, dryness, pruritus, and scaling were self-limited and transient.

DISCUSSION

The picosecond 755-nm Alexandrite laser has been postulated to improve the appearance of pores through neocollagenesis as a sequalae of laser-induced optical breakdown (LIOB). According to the theory of LIOB for skin revitalization, intraepidermal vacuolization is created inside the focused high-fluence zones within the epidermis as a result of laser energy absorption.[11,15] As a result, collagen remodeling and production of mucin and elastic tissue triggered by LIOB lead to the improvement of skin texture, wrinkles and pigmentation.[11,14] The new collagen is assumed to lift the depressions in the skin which helps improve the overall appearance of acne scarring and pore size. The use of DLA with a spot size of 6 mm has been reported to be most effective in safely improving pore size as it permits for the fractional delivery of energy within the confinement of a high fluence perimeter in the context of a low fluence background.[14]

To the best of our knowledge, this is the first retrospective study evaluating the effects of the 755-nm picosecond laser with DLA on pore size in Fitzpatrick skin type I-III. Although the effect of the picosecond 755-nm Alexandrite laser on pore size reduction was visibly observed in several studies,[12,15] this current study is the first to demonstrate clinically significant improvement in objective measures of pore reduction. Specifically, the results show that as little as two treatments delivered at 4 week intervals were effective in pore size reduction via score and percentile rank. Further, pore count reduction was sustained at the follow-up encounter, which was at time 4. However, because only one patient presented for their fourth visit thus far, the continued results of pore improvement need to be further investigated.

Although the mechanism of pore enlargement is not entirely understood, three main reasons include excessive sebum production, decreased skin elasticity around pores and increased follicular volume.[16] Some known risk factors for pore enlargement as a sequalae of aging include both genetic eg, intrinsic aging and environmental factors eg, extrinsic aging.[17] Adopting a stricter inclusion criteria to limit exposure to exogenous factors coupled with more rigorous standardization in regards to post-laser treatment care may control for confounding environmental variables such as UV exposure and adherence to skin protective measures. It would be interesting to examine if the use of broad-spectrum sunscreen and frequency of application as well as protective clothing/accessories such as wide brim hats may play a role in the efficacy of the 755-nm Alexandrite picosecond laser on pore size, and subsequently, if the results are maintained at regular follow-up visits. These environmental factors can play a role in undermining the effects of the 755-nm Alexandrite picosecond laser on pore quality in patients who geographically have more UV exposure from closer proximity to the equator or from lifestyle practices eg, tanning beds and nonadherence to skin protective measures.

At the conclusion of enrollment, 7 participants presented for their three month follow up visit. Participants who received less than three treatments likely showed evidence of pore size reduction secondary to transient tightening/edema. However, the significant improvement of pores demonstrated by score and percentile rank between times 1 and 3 suggest neocollagenesis, which is observed at three months the earliest.

This study consisted of a sample of *N*=32, had a short follow-up period, lacked a physician or patient evaluated scale and patient satisfaction with treatment. Lack of a control, split-face comparison and adherence to sunscreen may contribute to clinical improvement of pores. A larger sample size with longer follow-up time and inclusion of patients with skin type IV in addition to I to III, may provide further information on the efficacy and safety of picosecond laser treatment.

CONCLUSION

Future studies should investigate the long-term effect of 755-nm Alexandrite picosecond laser on pore size reduction as continued patient recruitment and data collection is necessary to comprehensively discern the 755-nm Alexandrite picosecond laser debate. Thus, prolonged follow past three months post treatment should be evaluated in order to determine if results are maintained. Nonetheless, the 755-nm Alexandrite picosecond laser shows promising results for the improvement of skin pores thus far.

DISCLOSURES

The authors declare no conflicts of interest.

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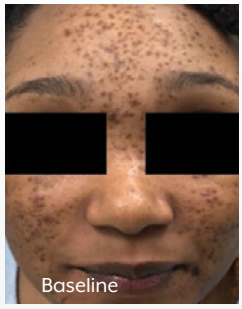

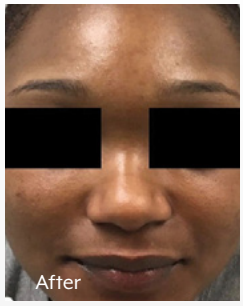

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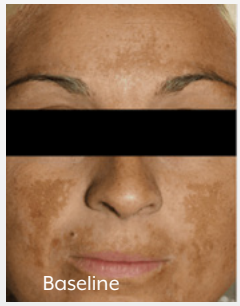

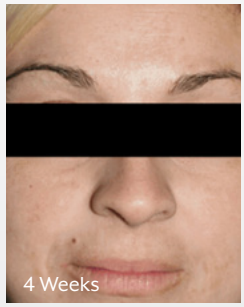

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December 2021 1308 Volume 20 • Issue 12

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Unna Boot With Keystone Advancement Flap Leads to Excellent Outcomes for Lower Extremity Reconstruction

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ABSTRACT

Background: The reconstruction of lower extremity defects can be technically challenging. The keystone island perforator flap is a workhorse reconstructive option for difficult-to-repair regions, including the lower limb. The goal of this study is to evaluate outcomes using the keystone flap in combination with the zinc oxide compression dressing (Unna boot) for repair of lower extremity defects.

Methods: We retrospectively evaluated 96 patients who underwent resection of malignancies or atypical neoplasms on the lower legs. A total of 114 defects were repaired with the keystone flap in combination with the Unna boot. Post-operative outcomes were assessed.

Results: The combination of the keystone flap with postoperative Unna boot application led to excellent outcomes. There was no association between complication rates and patient co-morbidities.

Conclusion: The combination of the keystone flap with the Unna boot is a safe and efficacious approach for reconstruction of lower extremity defects.

J Drugs Dermatol. 2021;20(12):1308-1312. doi:10.36849/JDD.5915

INTRODUCTION

Reconstruction of lower extremity defects following resection of cutaneous tumors is clinically and technically challenging.[1] The lower limb has poor skin laxity and scarce subcutaneous tissue, which contributes to the complexity of surgical repair. Ambulation introduces sheer forces that hinder healing, while the increased hydrostatic forces exerted on the limb during movement promote hematoma and seroma formation.[2] As a consequence of these factors, wounds on the lower limb have increased rates of infection and prolonged healing times.[1,3,4]

The anatomical and physiological factors predisposing patients to potential complications must be considered when selecting a repair method for defects of the lower extremities.[1,5] The lower limb's limited skin laxity and scarce subcutaneous tissue contributes to frequent dehiscence of primary linear closures.[6,7] Alternatively, secondary intention healing (SIH) eliminates the risk of dehiscence, but carries an increased risk of bleeding, scar contracture and prolonged healing time.[8] While multiple studies demonstrated the efficacy of split-thickness skin grafts (STSGs) and full-thickness skin grafts (FTSGs) in repairing lower extremity defects, grafts on the legs are associated with unfavorable outcomes, ranging from scarring to graft failure. Furthermore, poor vascularity in the lower third of the leg predisposes the region to higher complication rates.[1,4,9] Ambulation increases hydrostatic and sheer forces, promoting seroma and hematoma formation, as well as jeopardizing graft imbibition and inosculation. Many physicians recommend immobilizing the affected limb for several days to decrease graft failure.[8,10,11] However, even short post-operative immobilization can increase the risk of deep vein thrombosis, pulmonary embolism, and physical deconditioning, especially among the elderly or those with pre-existing co-morbidities.[5,8,10,11] Additionally patient compliance with immobilization can be difficult to monitor and enforce in an outpatient setting. Despite various graft modifications, including delayed grafting and quilting the graft to the wound bed, lower extremity grafting remains challenging with high rates of graft failure.[9,11-13]

In recent years, the keystone flap has emerged as a versatile reconstructive approach for defects of varying sizes on the head and neck, trunk, and extremities.[10,14,15] As described by Felix Behan, the keystone flap is a local fasciocutaneous flap that relies on perforator vessels for a robust vascular supply.[3,14] The flap incorporates the musculocutaneous and fasciocutaneous perforators, promoting increased flap viability and survival, while minimizing tension and subsequent risk of dehiscence and necrosis, making it ideal for reconstruction in areas with low tissue laxity.[6] Several keystone flap modifications have been described for regions requiring greater tissue recruitment, such as leaving the skin bridge intact to enhance flap survival and utilizing only the unilateral portion of the traditional keystone design,[5,16] with several reports promoting the keystone flap for repair of lower extremity defects following dermatologic surgery.[3,5,13,17,18]

To expand on the benefits of the keystone flap, we combined the keystone flap with the post-operative application of the zinc oxide-based compression dressing (Unna boot) following resection of cutaneous lesions on the lower leg. The Unna boot provides a compressive healing environment. Zinc promotes wound healing by increasing epithelialization and decreasing wound debris, while zinc's anti-inflammatory and antibacterial properties may reduce healing complications.[19-23] While both compressive and occlusive dressings have been utilized in the management of lower extremity wounds, Unna boots provide an optimal wound healing environment while minimizing required daily care, ultimately leading to high patient satisfaction.[24]

MATERIALS AND METHODS

Following Institutional Review Board approval, a retrospective chart review of all below-the-knee cutaneous malignancies undergoing surgical excision or Mohs micrographic surgery (MMS) was performed. All records between January of 2011 and September of 2018 at Weill Cornell Medicine/New York Presbyterian Hospital were reviewed. Patients were identified using electronic medical records and were cross-checked with the surgeons' case logs. Patients under the age of 18 were excluded from this study. All included patients received weekly post-operative zinc oxide compression dressings (Unna Boot) for 2-3 weeks until suture removal. All reconstructions were performed by one dermatologic surgeon (KM).

Complications assessed included the presence of culture-positive infections, dehiscence, seroma, pain, swelling, numbness, transient neuralgia, burning sensation, discoloration, erythema and hypertrophic/keloid scarring. The keystone flaps were also assessed for flap loss (complete vs partial flap loss). Wounds that were concerning for infection were cultured and treated appropriately.

Descriptive statistics of patient demographics, clinical characteristics and comorbidities were reported. Continuous variables were reported as mean ± SEM or median [25^{th};75^{th} percentile) and compared between reconstruction methods using the two-sample t-test or Wilcoxon rank-sum test, respectively. The chi-square or Fisher's exact test, as appropriate based on expected cell sizes, were used to assess the association between complications and patient characteristics with known status including sex, smoking status, initial pathology, and other discrete variables for each reconstruction method. The small number of complication events did not allow for the use of multivariable methods. All *P*-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 3.3.1 (R Core Team, Vienna, Austria) and Prism 8.0.0.

RESULTS

A total of 114 cases across 96 patients were reconstructed with variations of the keystone flap design were included in this study (Table 1). Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were the most common diagnoses: SCC and BCC comprised 47.4% and 35.1% of the cases, respectively. The mean defect area was 3.98 cm^2 in the keystone cohort and the mean reconstruction area was 42.20 cm^2. The mean number of Mohs stages necessary to achieve a clear margin was 2 stages (Table 1). The median follow-up time was 23.8 weeks.

The primary outcome in this study was the complication rate following keystone flap for reconstruction of lower extremity defects. The keystone flap had an overall complication rate of 7.9%

TABLE 1.

Patient Demographics and Defect Repair Characteristics	
	Keystone (N=114)
Total Participants	96
Male, N (%)	47 (49.0%)
Age at procedure (Y), median [IQR]	74.5 [64.8;82.0]
Average follow up time (Wk), median [IQR]	23.8 [8.97;57.5]
Smoking status, N (%)	
Current	7 (7.29%)
Former	29 (30.21%)
Never	58 (60.42%)
Unknown	2 (2.08%)
Patients with Diabetes, N (%)	9 (9.38%)
Patients with Heart Disease, N (%)	61 (63.54%)
Patients with PVD, N (%)	4 (4.17%)
Patients on Anticoagulants, N (%)	39 (40.63%)
Patients Receiving Prophylactic Antibiotics, N (%)	48 (50.00%)
Diagnosis, N (%)	
Atypical Nevus	6 (6.25%)
BCC	40 (35.09%)
Melanoma	10 (8.77%)
Other	4 (3.51%)
SCC	54 (47.37%)
Defect area (cm^2), median [IQR]	3.98 [2.45;5.84]
Reconstruction area (cm^2), median [IQR]	42.2 [32.40; 63.20]
Number of Mohs stages, mean ± SEM	2.00 ± 0.07

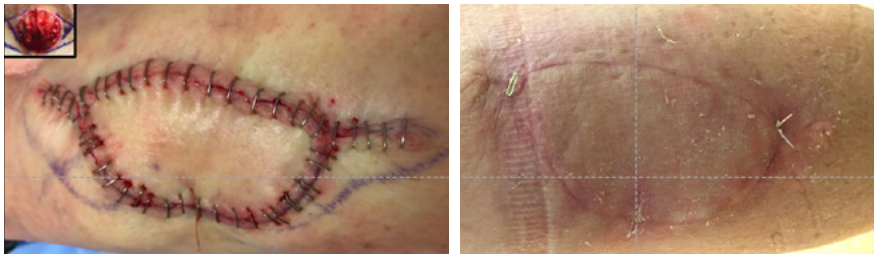
TABLE 2.

Post-Operative Complications	
	Keystone (N=114)
Complication, N (%)	9 (7.89%)
Infection, N (%)	8 (7.02%)
Dehiscence, N (%)	8 (7.02%)
Other Complications, N (%)	3 (2.63%)

TABLE 3.

Association of Patient Characteristics and Co-Morbidities and Postoperative Complications in the Keystone Cohort (reported per case)			
	Cases with complications (N=9)	Cases without complications (N=105)	*P* value
Age at Procedure, (Y), median [IQR]	73 [68.0; 82.0]	75.0 [63.0; 82.0]	0.84
Smoker			
Current	0 (0.00%)	8 (7.62%)	0.82
Former	3 (33.33%)	30 (28.57%)	
Never	6 (66.67%)	65 (61.90%)	
Unknown	0 (0.00%)	2 (1.90%)	
BMI (known status)			
Obese	0 (0.00%)	16 (15.24%)	0.20
Overweight	2 (25.00%)	28 (26.67%)	
Normal/Underweight	6 (75.00%)	36 (34.29%)	
Patients with Diabetes, N (%)	1 (11.11%)	12 (11.43%)	1.00
Patients with Heart Disease, N (%)	3 (33.33%)	70 (66.67%)	0.07
Patients with PVD, N (%)	1 (11.11%)	3 (2.86%)	0.30
Patients on Anticoagulants, N (%)	3 (33.33%)	45 (42.86%)	0.73
Pathology, N (%)			
Atypical nevus	1 (11.11%)	5 (4.76%)	0.02
BCC	1 (11.11%)	39 (37.14%)	
Melanoma	0 (0.00%)	10 (9.52%)	
SCC	5 (55.56%)	49 (46.67%)	
Other	2 (22.22%)	2 (1.90%)	
Repair Type, N (%)			
Keystone (Traditional, Modified)	4 (44.44%)	42 (40.00%)	1.00
V-Y Hemi-keystone Advancement Flap	5 (55.56%)	63 (60.00%)	
Reconstruction Area			
0–2 cm^2	2 (22.22%)	18 (17.14%)	1.00
2–4 cm^2	4 (44.44%)	45 (42.86%)	
≥4 cm^2	3 (33.33%)	42 (40.00%)	
Number of Mohs stages, mean ± SEM	2.00 ± 0.22	2.00 ± 0.07	1.00

FIGURE 1. Keystone advancement flap for repair of a surgical lower extremity defect. 73-year-old female with a 3.5 x 3.2 cm melanoma in situ on the calf was treated with staged excision with 5 mm margins to the level of the deep subcutis. The 4 x 4 cm postoperative defect (inset) was repaired with a keystone advancement flap with post-operative Unna boot application. At follow up, the patient has returned to her normal exercise activities. Two tip sutures are noted.



13 x 11 cm reconstruction with keystone flap

Follow-up at 1.5 months

No partial or complete flap losses were observed among those receiving keystone flaps. Among keystone flap cases, patients' clinical characteristics were not significantly associated with development of complications (Table 3). Age (P=0.84), smoking status (P=0.82), body mass index (BMI) (P=0.20), heart disease (P=0.07), anticoagulant use (P=0.73), peripheral vascular disease (PVD) (P=0.30), and diabetes (P=1.00) were not associated with development of complications. The total area of reconstruction (P=1.00) and number of Mohs stages (P=1.00) did not impact the development of complications following reconstruction with the keystone flap. There was a significant association between the pathology of the lesion and development of complications (P=0.02). Patients who had keystone procedures following resection of SCC had higher complication rates compared to other pathologies.

DISCUSSION

Wound healing following dermatologic surgery on the lower extremity can be a major source of frustration for patients. Many patients develop reactive edema and inflammation, and subsequently report swelling, pain, and frustration with the slow healing process.[24] In our experience, the Unna boot offers several advantages in the recovery setting, including minimizing the required wound care, while keeping the wound moist and reducing edema. Compared to standard dressings, Unna boot requires weekly (as opposed to daily) changes and provides rigid and constant wound compression which decreases edema and pain.[18,24,25] In this study, we demonstrate that the combination of the keystone flap with post-operative Unna boot application following lower extremity reconstruction leads to excellent clinical outcomes and enables same-day ambulation in older adults.

Factors associated with complications within the keystone cohort were evaluated. The keystone cohort had an overall complication rate of 7.9%, which is lower than a previously reported 9.6% complication rate from a systematic review of 282 keystone flap reconstructions for lower extremity defects.[17] The lower rate of complications in our cohort could be attributed to the combination of the keystone flap and the postoperative Unna boot application. Wound infections, while relatively uncommon following dermatologic surgery, occur more frequently in the lower extremities compared to other sites.[4] The surgical site infection rate (SSI) in our keystone cohort was 7.0%, which is consistent with previously published rates of SSI in lower extremity keystone flaps (2%-20%).[17,26] This is not surprising, as it has been previously reported that below the knee defects carry higher complication rates compared to other regions.[4] All of the infections resolved upon administration of antibiotics, and there were no subsequent complications. Wound dehiscence and flap necrosis can occur in regions with high wound tension, poor vascularization, or after infection. None of the patients in the keystone cohort experienced flap necrosis. The wound dehiscence rate in our cohort was slightly higher than that reported in this systematic review (5.7%). However, 7 out of 8 cases of dehiscence had a co-occurring infection, suggesting that the infection may have contributed to the dehiscence.

Many dermatologic surgeries are performed in elderly patients with other conditions conferring increased skin fragility and increased rates of complications. Our patient cohort had a median age of 74.5 years, supporting the efficacy of this technique in elderly patients. Co-morbidities, including PVD, edema, and diabetes mellitus, can exacerbate loss of skin durability in elderly patients and further complicate wound healing.[27,28] However, our analysis did not demonstrate an association between these co-morbidities and complications in the keystone flap cohort, suggesting this approach is a safe reconstructive technique in elderly patients, and patients with PVD, heart disease, and diabetes. Furthermore, while smoking is a known risk factor for wound dehiscence and flap necrosis, smoking status did not correlate with a higher complication rate in our cohort.

Patients in our study ambulated the same day. A previous series evaluating lower leg region keystone flap reconstructions following excision of melanomas demonstrated rapid mobilization following the procedure, with a median hospital stay of one night, which was required for bed rest and limb elevation.[5] The patients in our study ambulated immediately following the procedure without subsequent flap loss or flap necrosis, supporting the combination of keystone flap and Unna boot as a superior method that allows patients to rapidly return to their daily activities while minimizing use of hospital resources.

The findings in this study are subject to the inherent limitations of the retrospective analysis. A prospectively randomized clinical trial is necessary to validate the outcomes of the combination of the keystone flap with the Unna boot compared to the keystone flap alone. Additionally, the small number of keystone cases that developed complications limits the statistical power in determining the correlation between clinical parameters and complications. As such, a larger-scale study is needed to verify which clinical parameters correlate with a higher risk of complications when utilizing the keystone procedure.

Reconstructing lower extremity defects can be challenging and necessitates an individualized approach for each patient. This study demonstrates that the keystone flap in combination with the Unna boot is an excellent approach for reconstruction of post-surgical lower extremity wounds. The keystone flap in combination with postoperative Unna boot is an efficient, reliable and effective method for reconstruction of lower extremity defects, allowing for immediate post-operative mobilization and yielding excellent surgical outcomes.

DISCLOSURES

The authors have no conflicts of interest to declare.

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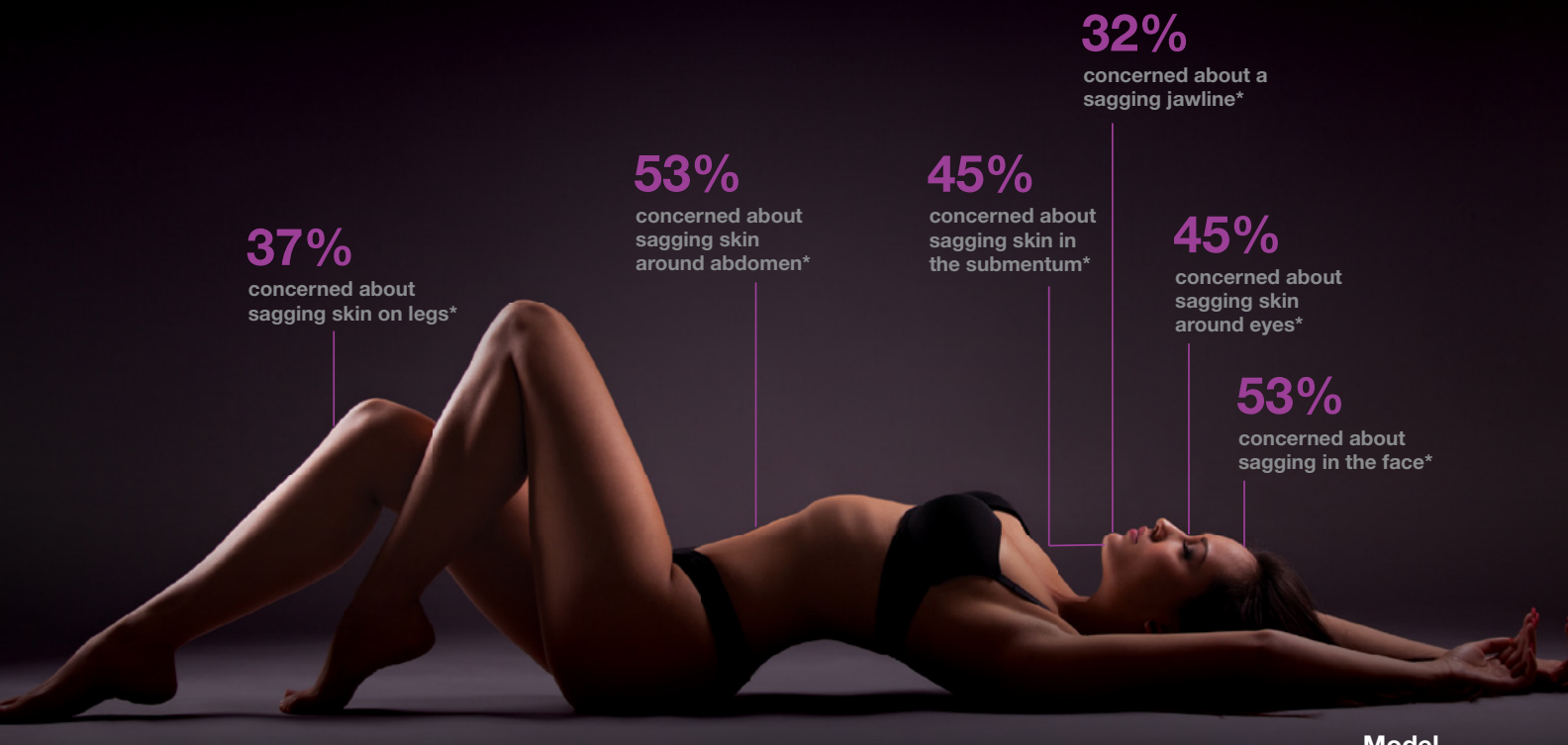

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Clinical Study to Evaluate the Efficacy and Tolerability of Cosmeceuticals Targeting the Dermal-Epidermal Junction

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ABSTRACT

Objective: The dermal-epidermal junction (DEJ), composed of rare proteins, plays a significant role in facial skin aging. A newly enhanced multi-ingredient anti-aging facial moisturizer (MFM) and eye cream (MEC) were formulated to target DEJ-related aging. The objective of this study is to assess the efficacy and tolerability of a dual-product regimen MFM and MEC as a treatment in improving intrinsically and extrinsically aged facial and periorbital skin.

Method: Forty-two female subjects, 42 to 65 years, Fitzpatrick skin type I–VI, with mild to moderate droopy eyelids, moderate crow's feet wrinkles, and moderate global photodamage completed this institutional review board (IRB)-approved study. Subjects applied the MFM and MEC twice-daily for 12 weeks. Clinical grading of efficacy and tolerability parameters, VISIA®-CR imaging, image analysis of wrinkles, skin pH, Tewameter, and pinch recoil measurements were performed at baseline, weeks 4, 8, and 12. Optical coherence tomography (OCT) imaging was performed at baseline and week 12.

Results: Statistically significant improvement was shown in both clinically graded parameters and bio-instrumentational analyses at all time points. Both products were well tolerated by subjects.

Conclusion: This IRB-approved clinical study demonstrated effectiveness in improving intrinsic and extrinsic signs of the global face and periorbital eye area aging after twelve weeks of twice-daily application.

J Drugs Dermatol. 2021;20(12):1314-1321. doi:10.36849/JDD.6355

INTRODUCTION

Aging of the facial skin is predominantly controlled by both intrinsic factors, such as age-dependent degradation of skin structure, and extrinsic factors such as environmental stressors.[1] Intrinsic and extrinsic aging of the facial skin can be visibly observed through outward signs such as fine lines, wrinkles, reduction in radiance, increase in redness, visual and tactile roughness, decrease in firmness, and visible pigmentation.[1,2]

The dermal-epidermal junction (DEJ), also known as the basement membrane, is a highly specialized structure located at the interface between cells and connective tissue.[1,2] This junction is primarily composed of proteins including collagen IV, collagen VII, Laminin 5, fibronectin, and integrin.[1,2] Intrinsic and extrinsic aging lead to a breakdown of the DEJ, a reduction in the rare proteins, a flattened appearance with reduced surface area and shortened rete ridges, loss of structural integrity, impaired communication between tissues, impaired skin adhesion, and increased skin fragility.[1,2] Thus, the skin functions sub-optimally. Due to these findings, it can be concluded that the DEJ is a structure worthy of investigation and treatment.[1,2] Previous reports have also shown that the facial skin is thicker in comparison to that of the periorbital area, which displays some of the body's first signs of aging.[2] As aging progresses, eyelid hooding, crepiness of the periorbital area, and crow's feet occur.[1-3] Therefore, a cosmeceutical treatment specific to the periorbital region must be formulated in such a way that not only addresses the DEJ, but also accounts for its structural difference to that of the global face.

While there is a multitude of literature centered on the deterioration of the DEJ, there still exists a need for cosmeceutical products that stabilize the junction by stimulating the synthesis of proteins at the DEJ. Previously, two cosmeceutical products

were formulated with aims of treating the DEJ on the global face and the eye area in order to improve signs of aging.[4,5] The face moisturizer was formulated with unique ingredients to address their respective concerns: *Astralagus membranaceus* root extract containing phytocompounds to promote wound healing;[6] Ursolic acid to inhibit photoaging induced by UVA light;[7] and tetrahexyldecyl (THD) ascorbate to serve as an efficacious and stable form of vitamin C for the purpose of treating aging skin.[8] A twelve-week clinical study demonstrated efficacy with an improvement in fine lines, evenness of skin tone, visual roughness, and overall facial skin appearance.[4] Similarly, an eye cream was formulated with the following ingredients to address their respective concerns: dipalmitoyl hydroxyproline to promote interaction between fibroblasts and the extracellular matrix,[9] Sunflower Seed Oil Unsaponifiables to reduce dryness by stimulating lipids and improving skin barrier and skin roughness due to its rich content in linoleic acid;[10] as well as THD ascorbate.[8] A twelve-week clinical study of using this eye cream twice-daily demonstrated efficacy with an improvement in fine lines, firmness, and elasticity of the periorbital area.[5]

The MFM and MEC were recently further enhanced with new technology to promote the synthesis of DEJ proteins and to stabilize global facial and periorbital skin. This includes rhamnose and silanol to further stimulate production of DEJ proteins and prebiotic, alpha glucan-oligosaccharide, and postbiotic *Pseudoalteromonas* ferment extract to balance and diversify the facial skin microbiome.[11-13]

This open-label study hypothesized that the two cosmeceutical multi-ingredient anti-aging products with enhanced formulations would effectively treat women with mild to moderate droopy eyelids, moderate crow's feet wrinkles, and moderate global facial photodamage over the course of twelve weeks, with twice-daily use, while maintaining tolerability. The objective of this study was to evaluate the efficacy and tolerability for use of the enhanced MFM and MEC.

MATERIALS AND METHODS

Subjects

This single-center, open-label, IRB-approved study was conducted between September 2020 and January 2021, with a clinical trial identifier of NCT04911374. Forty-five subjects between ages 35 to 65 years were recruited and 42 completed the trial. Recruited subjects fell in the range of Fitzpatrick skin type I–VI, had mild to moderate droopy eyelids, moderate crow's feet wrinkles, and moderate photodamage based on a modified Griffiths' ten-point scale[14] (Table 1). Exclusion criterion included subjects which were pregnant, nursing, or planning a pregnancy, had undergone any cosmetic facial procedures administered by a physician or skin care professional within the past six months, or had demonstrated hypersensitivity reaction to skincare products.

Ethical Considerations

The study protocol and informed consent documents were approved by the IRB. All subjects were given verbal and written information about the study and provided written informed consent before enrollment.

Study Procedure

A one-week washout period was required of qualified subjects prior to baseline in which they used a Gentle Cleansing Lotion (Revision Skincare®, TX, USA) and Aveeno Face Milk SPF 40+® (Johnson & Johnson Consumer Inc, NJ, USA).

TABLE 1.

Modified Griffith's 10-point Scale Used by the Clinical Graders to Evaluate Subjects at Baseline and Weeks 4, 8, and 12.

Parameter	Locations	0 =	9 =
Fine lines	Forehead, crow's feet area, global face	None	Numerous fine lines
Wrinkles	Forehead, crow's feet area, global face	None	Numerous, deep wrinkles
Droopy eyelid	Upper eyelids	None	Severe, droopy appearance
Upper eyelid appearance	Upper eyelids	Upper lid shows tight, lifted appearance	Severe, upper lid shows extreme sagging
Crepiness	Lower eyelids/under eye area	Skin appears smooth with no "crinkling"	Prominent, extensive "crinkly" texture
Roughness/smoothness (tactile)	Global face	Smooth, even feeling skin texture	Rough, uneven-feeling skin texture
Firmness (tactile)	Global face	Skin feels thick, dense, and firm	Skin feels thin and loose
Radiance/luminosity	Global face	Radiant, luminous or glowing appearance	Dull/matte and/or sallow skin appearance
Overall photodamage	Global face	None or minimal visual evidence of photodamaged skin	Severely photodamaged skin

At baseline, subjects were instructed to cleanse the facial skin using a provided Gentle Cleansing Lotion (Revision Skincare®, TX, USA), and apply both treatments twice daily (morning and evening). The MFM was applied to the entire face and the MEC was applied to both right and left periorbital areas including the under eyes, upper and lower eyelids, and crow's feet areas. Subjects were then instructed to apply the provided sunscreen and reapply throughout the day as needed. Additionally, subjects were instructed to document product application in a provided subject diary, which was collected at each visit and reviewed for compliance.

Outcome Clinical Measurements

Clinical evaluations of each subject (live-grading) were conducted during each visit by an expert clinical grader using the modified Griffiths' ten-point scale shown in Table 1. Additionally, photo-grading by a board-certified dermatologist was conducted on VISIA®-CR Standard Light Images at baseline, weeks 8 and 12 using the modified Griffiths' ten-point scale (Table 1). Subjects completed a provided self-assessment questionnaire at each study visit to document self-evaluation of skin condition parameters.

Tolerability Assessment

Local cutaneous tolerability assessments of the global face and eye area were completed by both the investigator assessing irritation including erythema, edema, and dryness and subjects self-assessing burning, stinging, and itching. Tolerability assessments were performed at each time point. A four-point scale (0=none, 1=mild, 2=moderate, 3=severe) was used to assess each parameter accordingly.

Clinical Photography

Photography was performed via VISIA®-CR imaging to document each subject's global face during each visit. Each subject had right, left, and center-view full-face images photographed under standard light and parallel polarized light filters. To assess the count, length, width, area, and depth of wrinkles and fine lines on the under-eye area, VISIA®- CR images of each subject's left view taken under standard 3 lighting from each study visit were analyzed using Stephens Wrinkle Imaging using Raking Light (SWIRL), a clinically validated and published method for quantitative assessment of facial wrinkles.[15]

Bioinstrumentation Measurements

Triplicate pinch recoil measurements were performed to assess skin elasticity at the crow's feet. A single measurement was taken each at the right crow's feet and on the right cheek per subject per time point using Tewameter TM300 (Courage + Khazaka electronic GmbH, Germany) to measure transepidermal water loss (TEWL). Triplicate skin pH measurements using a Skin-pH Meter PH905 (Courage + Khazaka electronic, GMBH, Germany) were performed on each subject's left cheek to determine the tested product's effect on overall cutaneous pH value. At baseline and week 12, an Optical Coherence Tomography (OCT) scan was taken on a 6 mm x 6 mm area on each subject's right cheek using the VivoSight (Mickelson Diagnostics Ltd, Kent, England) multi-beam OCT system with EnFace mode and was analyzed for epidermal thickness.

Statistical Analysis

The Wilcoxon signed-rank test was performed on live-graded clinical efficacy parameters. A student t-test was performed on the photo-graded clinical efficacy parameters. To correct for multiple comparisons with baseline for photo-grading, the Bonferroni correction was used to adjust the cutoff value for significance with $P<0.025$. A Wilcoxon signed rank test was used to determine improvement in self-assessment values at each post-baseline timepoint.

A Wilcoxon signed-rank test was used to determine percent average change in pinch recoil time at each post-baseline timepoint, and to assess the change in wrinkle and fine lines count from baseline to week 12. A paired *t* test was performed for TEWL and skin pH measurements to determine the percent average change in TEWL and pH at each post-baseline timepoint; for OCT measurements to determine the change in epidermal thickness from baseline to week 12; and to assess the change in width, area, and depth of wrinkles and fine lines from baseline to week 12.

These analyses were performed using SAS (version 9.4). Statistical significance was achieved with $^{*}P\leq0.05$ and $^{**}P\leq0.01$, and highly statistical significance was achieved with $^{***}P\leq0.001$.

RESULTS

Study Subjects

Forty-two subjects with a mean age of 55.1 years (age range, 42–65 years) completed the study. The demographics of the completed study are shown in Table 2.

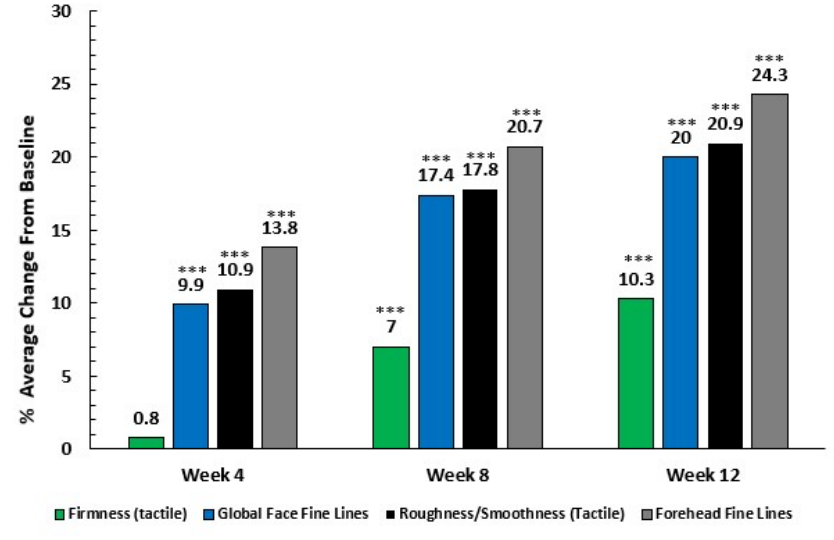
Clinical Grading Results

Clinical assessment via live grading demonstrated statistical significance at all time points for both the MFM and the MEC (Figures 1A and 1B). Specifically, after 12 weeks, the following highly statistically significant results were demonstrated: 85.7% of subjects showed an improvement in forehead fine lines with an average improvement of 24.3%, 90.5% of subjects showed an improvement in global face fine lines with an average improvement of 20%, 85.7% of subjects showed an improvement in tactile firmness of the facial skin with an average improvement of 10.3%, and 95.2% of subjects showed an improvement in tactile roughness and smoothness of the facial skin with an average improvement of 20.9% (Figure 1A).

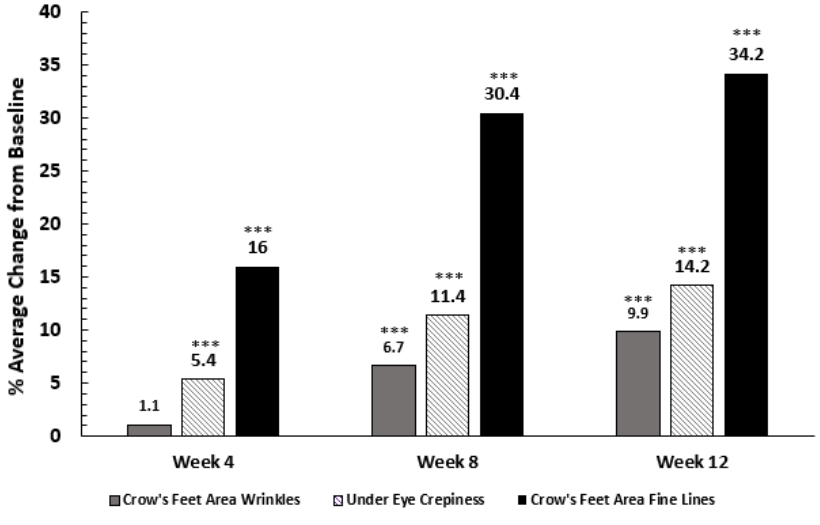
After 12 weeks of twice-daily usage of the MEC in the periorbital

FIGURE 1. Percent average change from baseline for clinical efficacy parameters at weeks 4, 8, and 12 assessed by the live clinical grader using the modified Griffith's 10-point scale for the multi-ingredient face cream (A). Percent average change from baseline for efficacy parameters at weeks 4, 8, and 12 assessed by the live clinical grader using the modified Griffith's 10-point scale for the multi-ingredient eye cream (B). Percent average change from baseline for efficacy parameters at weeks 8 and 12 assessed by the photo-grading using the modified Griffith's 10-point scale for both the MFM and MEM (C). Statistical significance was achieved at $^{*}P<0.05$ for live grading, $^{*}P<0.025$ for photo-grading.

(A)



(B)



(C)

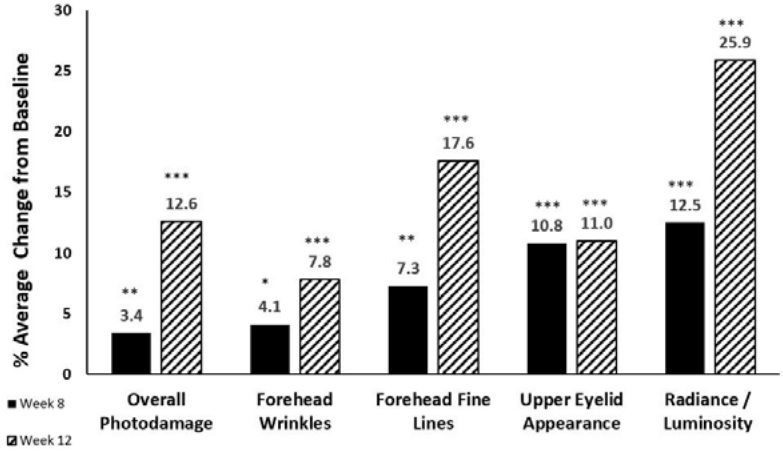


TABLE 2.

Demographics of Subjects Who Completed the Clinical Study		
	All Subjects	
Total Subjects	42	%
Age		
Mean	55.1	--
Standard Deviation	6.5	--
Minimum	42	--
Median	56	--
Maximum	65	--
Gender		
Female	42	100
Ethnicity Hispanic or Latino	4	9.5
Not Hispanic or Latino	38	90.5
Race		
Asian	7	16.7
Black or African American	3	7.1
White or Caucasian	32	76.2
Other	0	0
Fitzpatrick Skin Type		
I	1	2.4
II	22	52.4
III	14	33.3
IV	2	4.8
V	2	4.8
VI	1	2.4

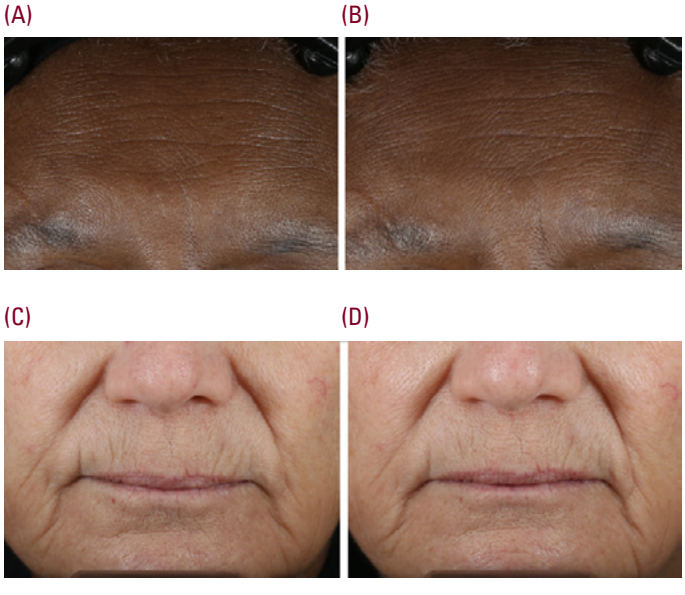
area, 87.5% of subjects showed an improvement in crow's feet area fine lines with an average improvement of 34.2%, 69% of subjects showed an improvement in under eye crepiness with an average improvement of 14.2% (Figure 1B).

Photo-grading measurements demonstrated statistically significant improvement at both 8 and 12 weeks (Figure 1C). After 12 weeks there was an average improvement from baseline of 7.8% in forehead wrinkles, 12.6% in overall photodamage, 17.6% in forehead fine lines, and 25.9% in full face radiance. The MEC demonstrated efficacy with an average improvement of 11% from baseline in the upper eyelid area appearance.

Tolerability Results

Both treatments were well tolerated by the subjects, as no statistically significant increase in scores for tolerability parameters were seen at any time point. There was one mild adverse event in the periorbital area that was resolved, and the subject was discontinued from the study.

FIGURE 2. VISIA®-CR clinical photography of subjects' respective facial areas at baseline (A, C), and week 12 (B, D). Clinical images were taken under parallel polarized light (A, B), and standard light (C, D). Female subject was 61 years old, Fitzpatrick skin type V (A, B). Female subject was 63 years old, Fitzpatrick skin type II (C, D).



Clinical Photography Results

Improvements in skin texture, fine lines, wrinkles, and radiance of both the face and eye area were demonstrated by VISIA®-CR photography. A reduction in forehead fine lines and wrinkles (Figures 2A and 2B) was observed in subjects, as well as improvement in marionette and vertical lip fine lines (Figures 2C and 2D). An overall global facial skin improvement was demonstrated with skin appearing healthier at week 12.

Improvements in upper eyelid appearance, crow's feet area fine lines, under eye fine lines and under eye crepiness (Figures 3A and 3B) were observed. There was a notable 8% average reduction in laxity of the upper eyelid after 12 weeks, as demonstrated by clinical grading. An increase in radiance, firmer skin, and healthier skin of the periorbital area (Figures 3C and 3D) was evident as well.

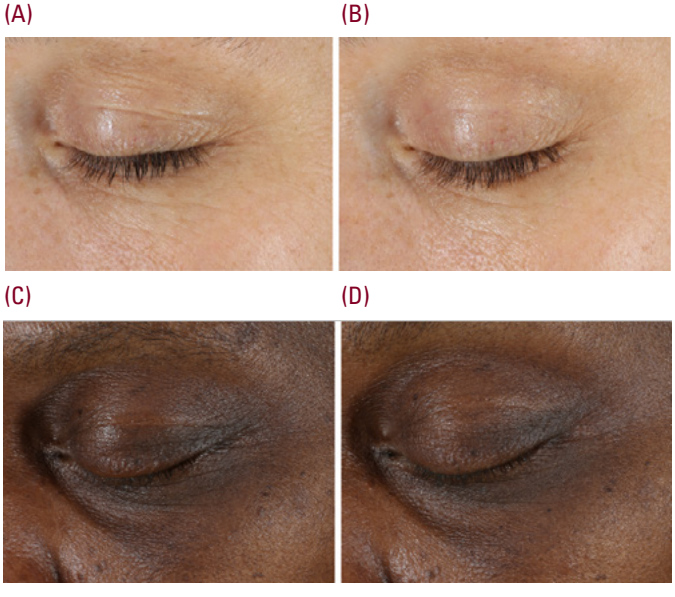
Self-Assessment Results

Most subjects responded favorably to self-assessment questions. Specifically, 73.8% of subjects reported that their skin appeared smooth and 71.4% of subjects reported that their under-eye area appeared bright after 12 weeks daily usage of MFM and MEC, respectively.

Bioinstrumentation Results

A statistically significant decrease in pinch recoil measurements on the left crow's feet area at week 12 was demonstrated

FIGURE 3. VISIA® -CR clinical photography under standard light of subjects' periorbital area at baseline (A, C, E), week 8 (D, F), and week 12 (B). Female subject was 60 years old, Fitzpatrick skin type II (A, B). Female subject was 42 years old, Fitzpatrick skin type II (C, D). Female subject was 60 years old, Fitzpatrick type V (E, F).



with an 4.8% average improvement (***$P \leq 0.001$). Tewameter measurements showed a statistically significant improvement inTEWL values on the crow's feet area at each post-baseline time point, as well as on the cheek at weeks 4 and 8 when compared to baseline. After 8 weeks, an average of 7.6% improvement on the cheek and 13% improvement on the right crow's feet area were observed (***$P \leq 0.001$). Skin pH measurements remained within skin neutral pH of 4.5 to 5.5.

FIGURE 5. Optical Coherence Tomography (OCT) photography on a 6 mm x 6 mm cross-section of epidermal thickness from right cheek at baseline (A) and week 12 (B). Female subject was 51 years old, Fitzpatrick skin type III.

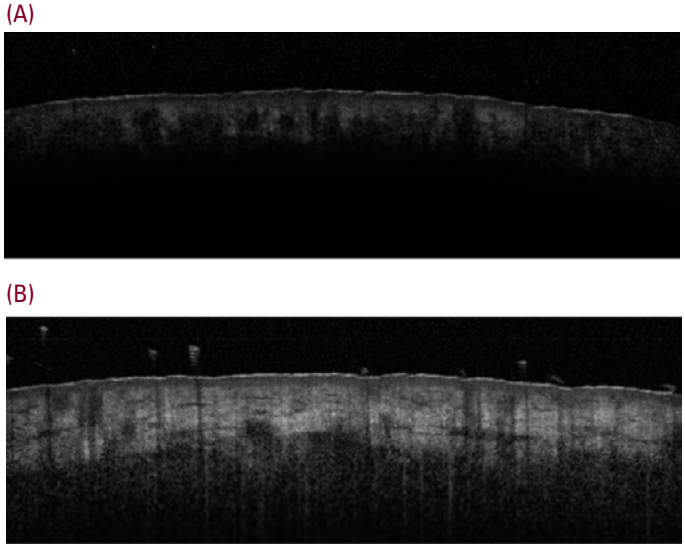
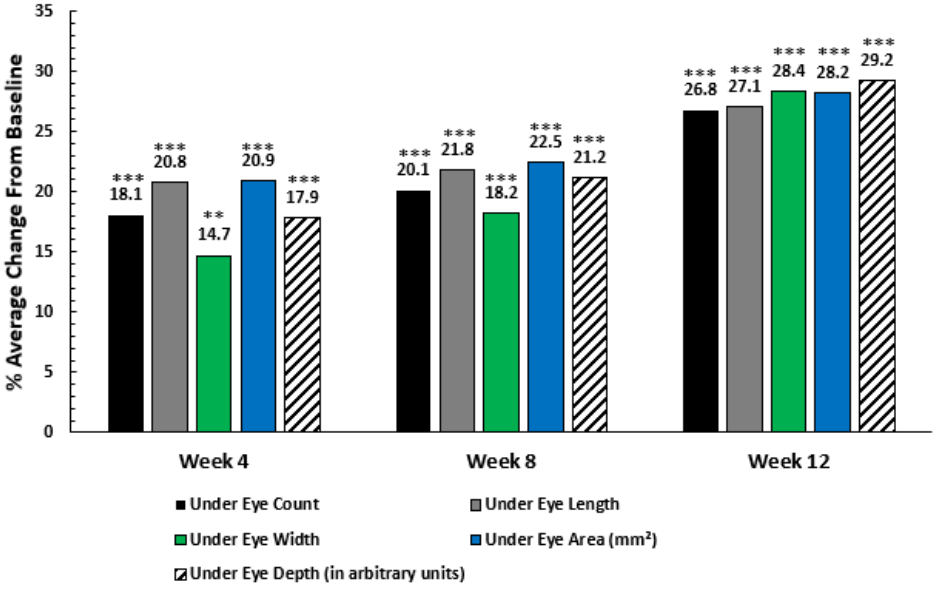


Image analysis of under eye fine lines and wrinkles demonstrated highly statistically significant results at week 12 compared to baseline values with 26.8% reduction in wrinkle count and 27–29% reduction in wrinkle length, width, area, and depth (Figure 4).

There was a 4.5% average increase in epidermal thickness after twelve weeks as measured by OCT. While this result did not achieve statistical significance, an improvement in epidermal, DEJ, and dermal features were demonstrated. For example, subject, 51 years of age showed improvement in epidermal thickness after twelve weeks (Figure 5).

FIGURE 4. Percent average change (improvement) from baseline for under eye raking light measurements at weeks 4, 8 and 12. VISIA®-CR images of each subject's left view were taken under raking light condition were analyzed using Stephens Wrinkle Imaging using Raking Light (SWIRL). Statistical significance was achieved at *$P<0.05$.



DISCUSSION

The DEJ is an integral structure in skin aging due to its significant contribution to the skin's mechanical stability.[1,2] There is an unmet need addressing aging at the DEJ. A predecessor MFM clinically demonstrated efficacy in patients with mild-to-moderate wrinkles and uneven skin tone.[4] Additionally, a radiofrequency (RF) microneedling-pairing case study with the MFM applied twice-daily for two weeks prior to and four weeks post-procedure demonstrated safety and tolerability.[16] The MFM was shown to promote healthier skin of the global face prior to RF microneedling, and the combination with RF microneedling demonstrated synergy. Furthermore, a previous version of the MEC clinically demonstrated efficacy in reducing signs of aging skin in the eye area, including the upper eyelid.[5]

These two cosmeceuticals were further enhanced with new technologies that target and stabilize the DEJ's architecture, treat photodamage, and target the skin microbiome. Rhamnose and silanetriol were incorporated to encourage the expression of collagen IV, VII, restore dermal papillae, and to improve epidermal thickness.[11,12] Previous studies have shown that the element silicon (Si) plays a role in collagen synthesis and is important in the architecture and organization of the skin.[11] Rhamnose, a natural sugar with good bioavailability, has demonstrated effectiveness in upregulating collagen IV, laminin, and inhibiting elastase.[12] *Pseudoalteromonas* ferment not only is a postbiotic which contains beneficial ingredients for the skin but also targets elastin and collagen I, III, and IV to improve skin elasticity and firmness.[13] Furthermore, the cosmeceuticals contain bioavailable peptide(s), botanical extracts, antioxidants, and a prebiotic (alpha glucan oligosaccharide).

Given the enhanced formulation it was not surprising that the present clinical study yielded favorable and statistically significant results. It was determined by live-grading that 95.2% of subjects showed an improvement in tactile roughness and smoothness of the facial skin, 90.5% showed an improvement in global face fine lines, and 87.5% showed an improvement in crow's feet area fine lines after twelve weeks. By week 12, subjects showed average improvements of 24.3% in forehead fine lines, 20.9% in tactile roughness and smoothness of the facial skin, and 34.2% in crow's feet area fine lines. Notably, photo-graded clinical parameters showed a two-fold increase in improvement between week 8 and week 12, whereas upper eyelid appearance at week 8 and 12 exhibited highly statistically significant improvement. Because the MEC was uniquely formulated to treat the sensitive and fragile upper eyelids, improvement in this area requires time and continued product usage. Lastly, the clinical parameter of forehead fine lines yielded different numerical results between live-grading and photo-grading. While both sets of results produced highly statistically significant values using the modified Griffith's scale, this difference may be attributed to natural bias that arises with subjective assessment.

A visual improvement in aging of the overall global face and periorbital area was demonstrated by VISIA®-CR images. Specifically, forehead, perioral and periorbital fine lines and wrinkles, and overall skin health were improved between baseline and each timepoint. Bio-instrumentational analyses showed a highly statistically significant improvement in elasticity at the crow's feet, a highly statistically significant improvement in TEWL, and a maintenance of skin neutral pH at each post-baseline time point. Furthermore, OCT measurements showed an increase in epidermal thickness, while raking light measurement of the under-eye area demonstrated improvement in all features. Lastly, self-assessment results indicate approval of the MFM and MEC by study participants.

Overall, results suggest that the enhanced MFM and MEC – fortified with bioavailable peptides, antioxidants, combined silanetriol and rhamnose technology, as well as a prebiotic and postbiotic – yield anti-aging results in women with mild to moderate droopy eyelids, moderate crow's feet wrinkles, and moderate global facial photodamage.

The limitations of this study were that neither a placebo, nor double blinded study procedure were utilized. Additionally, this study took place during COVID-19 and the investigators recognize that patients may have had sensitivity to facial coverings that could have influenced redness of the skin.

CONCLUSION

This twelve-week open-label, IRB-approved clinical study evaluated the efficacy and tolerability of the MFM and MEC in targeting facial and periorbital skin aging. Forty-two patients completed the study with no significant tolerability concerns after applying the MFM and MEC twice daily for twelve weeks, as confirmed by the investigator. It was demonstrated that these two cosmeceutical multi-ingredient anti-aging products with enhanced formulations were effective in treating women with mild to moderate droopy eyelids, moderate crow's feet wrinkles, and moderate global facial photodamage. Overall, the enhanced anti-aging MFM and MEC composed of anti-aging peptides, silanetriol, rhamnose, antioxidants, and prebiotic and postbiotic proved to be an effective solution in the treatment of facial and periorbital aging.

DISCLOSURES

Dr. Seemal R. Desai has performed clinical trials and consulting for a variety of different organizations and serves in multiple leadership capacities. Dr. Desai served as the clinical grader for this clinical trial. Dr. Jiang oversaw the execution of the clinical trial described in this manuscript and helped with image analysis and result interpretation. Dr. Zahr, and Ms. Kononov are employees of Revision Skincare. At the time of manuscript preparation, Ms. Addae was an employee of Revision Skincare.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Topical *S. aureus*-Targeting Endolysin Significantly Improves Symptoms and QoL in Individuals With Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic skin condition affecting an increasing number of children and adults whose quality of life is impacted by chronic itch and pain. It is characterized by an altered epidermal barrier, skin inflammation, and skin microbiome dysbiosis particularly over-colonization of *Staphylococcus aureus*. The efficacy and tolerance of a cream containing a *S. aureus*-targeting technology (endolysin) was assessed in an open-label, two-week study in children and adults with mild-to-moderate atopic dermatitis. A total of 43 patients ranging from 7 months to 57 years old were included and all patients finished the study without any tolerance problem. Disease severity, measured with SCORAD, quickly reduced by 43% in 7 days and by 68 % in 14 days. The benefit was perceived by the whole panel with a marked improvement in overall QoL. This study shows the efficacy of a highly specific *S. aureus*-targeted technology in alleviating symptoms and improving QoL in children and adults with atopic dermatitis. It could also be beneficial in reducing and preventing flares in subjects with *S. aureus* load due to its good tolerance and specific action.

J Drugs Dermatol. 2021;20(12):1323-1328. doi:10.36849/JDD.6363

INTRODUCTION

Atopic dermatitis (AD) affects 20% of infants and adolescents and up to 3% of adults worldwide[1,2] and its incidence is increasing globally.[3] AD causes erythema, constant intense itching,[4] and psychological distress[5] which negatively impacts quality of life (QoL) more than other chronic conditions such as heart disease or diabetes.[6] In children, it has the second highest impact on QoL.[7]

AD is a chronic inflammatory skin condition associated with epidermal barrier dysfunction, abnormal immune response, and skin microbiome imbalance.[8] These three factors are interdependent thus enabling AD symptoms to be managed from multiple angles. Skin microbiome dysbiosis is often characterized by low skin microbial diversity compared to healthy skin and an over-colonization of *S. aureus*.[9] *S. aureus* levels are associated with AD disease severity, flare frequency and symptoms that directly impact QoL.[10-12] Its toxins stimulate proinflammatory cytokine and chemokine production causing itching, burning sensations, and pain,[13,14] and create a vicious itch-scratch cycle.[15-17]

During AD flares, treatment aims to reduce inflammation and itching, rebuild the epidermal barrier, and prevent secondary infections.[18] Appropriate moisturizers and cleansers are the cornerstones of AD management to address skin barrier dysfunction.[19] Topical corticosteroids (TCS) are first-line treatment for flares since they effectively reduce inflammation.[20] However, their use is limited to avoid developing skin atrophy in sensitive skin areas.[21] Furthermore, patients express concerns (corticophobia) which can impact TCS use, adherence to treatment and overall effectiveness.[22] Secondary infection, particularly by *S. aureus*, can be treated with broad spectrum or anti-staphylococcal antibiotics[20] but these can damage the beneficial skin microbiota and potentially lead to antibiotic resistance.[23] Considering the mounting evidence pointing towards the major negative role of *S. aureus* in AD and the beneficial role of the skin microbiome for skin homeostasis, a treatment exclusively targeting *S. aureus* offers many advantages.[24]

Many microbial ecosystems, including the skin microbiome, harbor viruses called bacteriophages that only infect bacteria.[25] Bacteriophages are specific for their target bacteria, and at the end of their lytic cycle induce the production of enzymes, called endolysins, which degrade the peptidoglycan of the bacterial cell wall from within, causing cell lysis and progeny virion release. Since Gram-positive bacteria, such as *S. aureus*,

lack an outer membrane, the peptidoglycan is exposed and the appropriate endolysin applied externally can perforate the cell wall resulting in osmotically driven lysis and bacterial cell death.[26]

Endobioma™ is a recombinant chimeric protein derived from naturally occurring endolysin designed to be highly effective against *S. aureus*. Its structure combines a cell wall binding domain that specifically recognizes *S. aureus* peptidoglycan motifs and two enzymatically active domains that lyse them. Low doses of Endobioma have been shown to quickly eliminate *S. aureus*, including antibiotic resistant strains such as MRSA.[27,28] Other typical commensal skin residents, even from the staphylococci genera such as *S. epidermidis*, are left unaffected.[27,29]

The aim of this study was to evaluate the efficacy (disease severity and QoL) and tolerance of a cream containing Endobioma applied for two weeks in adults or children with mild-to-moderate atopic dermatitis.

MATERIALS AND METHODS

Study Product

The study product contained Endobioma, also known as Staphefekt™ SA.100, kindly provided by Micreos Human Health (Bilthoven,The Netherlands) in a 0.0035% simplex cetomacrogol formula.

In vitro Efficacy Against *S. aureus*

To evaluate the antimicrobial activity of the study product, a small aliquot was inoculated and homogenized with a suspension of *S. aureus* ATCC 6538 to achieve a final concentration of 10^6 colony forming unit (CFU) per gram of product. After 30- and 60-minutes contact time at room temperature, the mixture was neutralized to stop enzymatic activity. Serial dilutions were plated on Eugon LT100 agar plates, incubated at 35°C for 48 hours, and surviving *S. aureus* colonies on the plates counted.

In vivo Study Design

An open-label, interventional, clinical study was conducted in South Africa from September to October 2018, according to the Helsinki Declaration (1964) and its successive updates. Participants replaced their normal cream with the study product and applied it on all body lesions as needed but at least once daily for two weeks. Lipikar Syndet AP+ was provided for daily cleansing.

Participants

Patients were recruited from the IEC (Institut d'Expertise Clinique) database. To be included, male or female Caucasian adults (aged 18 to 70 years) or children (aged 3 months to 12 years) presented an AD diagnosis meeting Hanifin's criteria (>3 basic features and >3 minor features), with AD present for at least 6 months prior to inclusion (SCORAD >30 at inclusion).

Measurements

Clinical examinations were performed at baseline, day 7 and day 14. Cutaneous acceptability was assessed by observing physical signs (including erythema, oedema, dryness, desquamation) linked to the study product and questioning about functional signs (including tingling, tightness, and burning sensation) at baseline, day 3 (by phone), 7, and 14. The participants reported their nature, location, intensity, duration, period of appearance after product application. Application number and frequency were also reported.

On days 0, 7 and 14, disease severity was clinically evaluated using SCORAD (SCORing Atopic Dermatitis), and local SCORAD at defined areas. Standardized pictures of the AD lesion were taken on days 0, 3 (by the subject), 7, and 14, focusing on the lesion used for Local SCORAD. Participants completed Patient-Oriented SCORAD (PO-SCORAD) and ranked pruritus, tingling, and burning sensation on a scale from 0 (absent) to 3 (severe) on day 0, 3, 7, and 14. QoL was measured using DLQI (Dermatology Life Quality Index) and CDLQI (Children's Dermatology Life Quality Index) questionnaires on days 0, 3, 7, and 14.

Data Analysis

Mean and standard deviation were calculated for individual data at each time point and compared to baseline values. Significance thresholds were $P<0.05$ and $P<0.01$ for Shapiro-Wilk test. Distribution normality was checked with Shapiro-Wilk test, if distribution was normal, paired Student t-test was applied, and if not, the Wilcoxon test was used. Any statistically significant changes were reported with their corresponding variation from the individual percentage mean. Percentage of patients with improvement was calculated.

RESULTS

In vitro results showed that 1g of Endobioma formula rapidly inactivated 10^6 CFU of *S. aureus*. Within 30 minutes, 99.99 % of the bacteria were killed and the limit of detection was achieved after one hour. (Figure 1 >4-log CFU reduction)

FIGURE 1. Time-kill assay. Endobioma™-formula vs placebo.

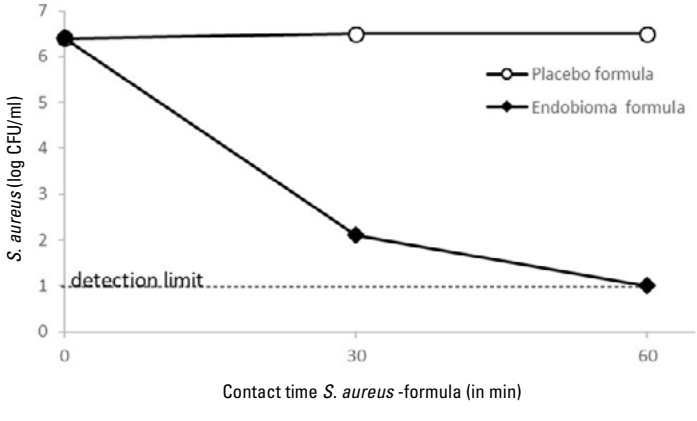


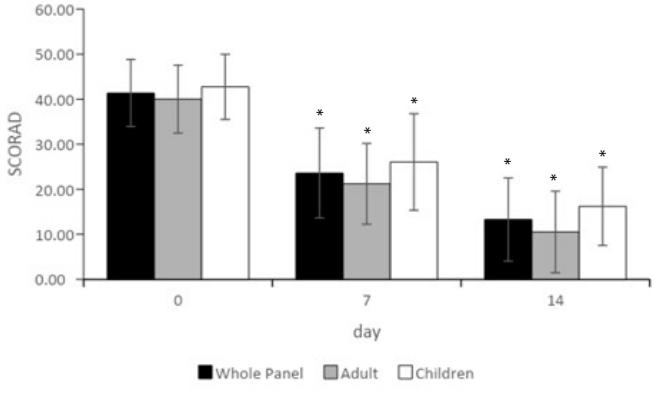
TABLE 1.

Panel Demographic			
	Whole Panel	Adult Panel	Children Panel
Patient, n	43	22	21
Female, n (%)	29 (67%)	19 (86%)	10 (48 %)
Male, n (%)	14 (33%)	3 (14%)	11 (52 %)
Mean age (min-max) years	20 (0.58-57)	33.7 (18-57)	5.7 (0.58-12)
SCORAD at baseline average ± SD	41.36 ±7.45	40.03 ±7.57	42.75 ± 7.24

In total, 43 people [22 adults (mean age, 33.7) and 21 children (mean age, 5.7)] were included and completed the clinical study, all presenting comparable disease severity at baseline (see SCORAD -Table 1). The participants reported applying the study product two to three times daily on average during the study period.

Overall, the study product was well tolerated, and no adverse events related to it occurred. Nine participants reported some cutaneous discomfort, redness, small pimples, or dryness, which were judged to be expected and frequently encountered in patients with mild AD.

FIGURE 2. Mean SCORAD scores with Endobioma™-containing cream in whole, adult, and children panels. Error bars indicate standard error of the mean.



*P<0,001 vs D0

The study product rapidly reduced disease severity in a

TABLE 2.

Clinical Scoring of Disease Severity Progression Over the Two-Week Study Period –Whole Panel (n=43)						
Clinical scoring of disease severity	Baseline Mean ± SD	Day 7 Mean ± SD	Day 14 Mean ± SD	D7/D0 variation	D14/D0 variation	% Patients with improvement at day 14
Score A (Extent)	14.6± 12.8	8.1*± 8.6	5.5*± 6.1	-39%	-58%	91%
Score B (Intensity)	6.5± 1.6	3.6*± 1.6	2.3*± 1.6	-44%	-65%	95%
Pruritus	7.8± 1.5	4.6*± 2.5	2.1*± 2.2	-41%	-74%	98%
Sleep loss	7.7± 1.6	4.7*± 2.5	2.1*± 2.1	-40%	-74%	98%
SCORAD Index	41.4± 7.5	23.6*± 10.1	13.3*± 9.2	-43%	-68%	100%
Local SCORAD	9.2 ± 1.7	5.3* ± 2.2	3.1* ± 2.2	-42%	-67%	100%

**P*< 0.001 versus Baseline

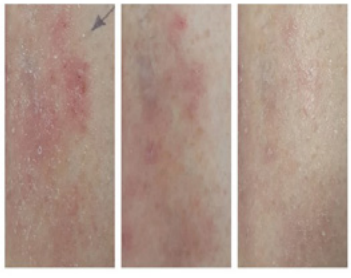
TABLE 3.

Self-Assessment Results Including PO-SCORAD and Skin Sensitivity Results –Whole Panel.				
	Baseline	Day 3	Day 7	Day 14
PO-SCORAD				
Mean ± SD % variation	49.9 ± 13.7	43.4 ±16.0** -11%	35.7 ± 17.0* -30%	25.7 ± 16.8* -50%
% patients with improved PO-SCORAD	--	65%	91%	100%
Skin sensitivity questionnaire				
Pruritus sensation Mean ± SD % variation	2.58 ± 0.50	1.86 ± 0.83* -26 %	1.84± 0.72* -29%	1.26 ± 0.88* -51 %
Tingling sensation Mean ± SD % variation	2.16 ± 0.75	1.33 ± 0.89* -33%	1.26 ± 0.66* -41%	0.74 ± 0.69* -63%
Burning sensation Mean ± SD % variation	2.4 ± 0.73	1.23 ± 0.95* -47%	1.33 ± 0.94* -46%	0.56 ± 0.83* -79%

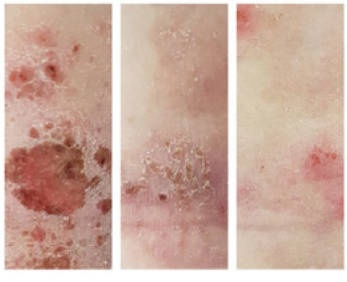
**P*<0.001, ***P*<0.005

FIGURE 3. Pictures of lesions treated with the Endobioma™-containing cream at baseline, day 7, and day 14 in an adult subject (3A) and a child (3B).

(3A) Subject nb41. SCORAD from 11 at Baseline to 2 at D14

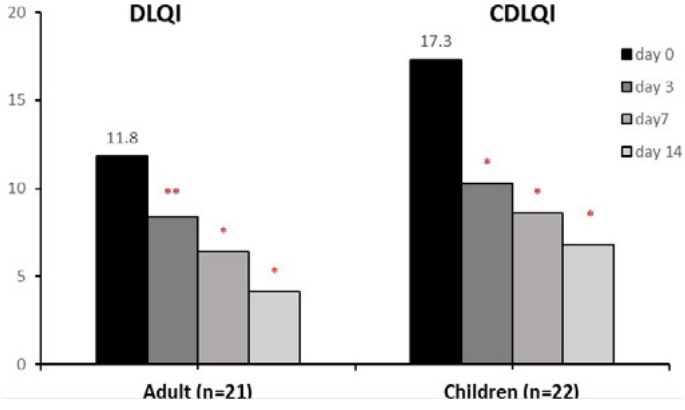


(3B) Subject nb38. SCORAD from 12 at Baseline to 5 at D14



statistically significant and clinically relevant manner over the two-week study. SCORAD scores reduced by an average of 43% (day 7) and 68% (day 14) compared to baseline (Figure 2). The treatment was equally effective in both adults and children with all patients improving by day 14. Similarly, local SCORAD reduced by 42% at day 7 and 67% at day 14 compared to baseline (Table 2). Visible lesion resolution is shown in Figure 3. Notably, as early as day 3, patients reported a statistically significant decrease in PO-SCORAD (Table 3). PO-SCORAD further decreased by an average of 30% (day 7) and 50 % (day 14) with all participants reporting better scores by day 14. More specifically, skin discomfort significantly improved by day 3 in both adults and children, with itching decreased by 51%, tingling by 63% and burning by 79% at day 14 ($P<0.005$ vs baseline) (Table 3).

FIGURE 4. Quality of life assessments.



*$P<0.001$, **$P<0.01$

The reported improvements translated into a significantly increased QoL for all participants: 100% of children and 95% of adults reported a higher QoL on day 14 with DLQI reducing from 11.8 ± 5.4 to 4.1 ± 4.0 in adults and CDLQI from 17.3±5.4 to 6.8±5.3 in children ($P<0.001$ vs baseline) (Figure 4, Table 4).

Participants reported a good cosmetic acceptability. After just 7 days, 98% of participants reported that the study product left a protective film on the skin and the skin felt comfortable. By day 14, all patients agreed that the study product was easy to apply with 91% wanting to continue using it.

DISCUSSION

For the first time, our study demonstrates the efficacy of an anti-*S. aureus* product in children and adults with AD. With Endobioma monotherapy, both clinicians and participants including children reported significantly improved skin sensitivity, PO-SCORAD and overall QoL. A recent Cochrane review[30] analyzed studies aiming to reduce *S. aureus* in AD patients and failed to correlate anti-staphylococcal intervention with improvement in symptoms and QoL especially in children. However, our results suggest that a precision ingredient like Endobioma alone could be a potential alternative to traditional

TABLE 4.

DLQI/CDLQI Results

	Baseline Mean ± SD	Day 3 Mean ± SD	Day 7 Mean ± SD	Day 14 Mean ± SD	D3/D0 variation	D7/D0 variation	D14/D0 variation	Patients with improvement on day 3	Patients with improvement on day 7	Patients with improvement on day 14
DLQI Adults N=21	11.8 ± 5.4	8.4**± 5.2	6.4* ± 3.8	4.1* ± 4.0	-26%	-42%	-63%	76%	86%	95%
CDLQI Children N=22	17.3 ± 5.4	10.3* ± 6.8	8.6* ± 5.9	6.8* ± 5.3	-43%	-51%	-61%	82%	91%	100%

*$P<0.001$, **$P<0.01$

treatments in AD adults and children. Using Endobioma as adjunctive therapy to boost efficacy of medical treatments and potentially reduce their length of use would be interesting and should be further investigated.

In this era of increasing antibiotic resistance, Endobioma mechanism of action makes it an attractive, precise, antimicrobial solution.[31] The recognition and lytic activity are highly specific to *S. aureus* cell wall, excluding impact on other bacteria even within the same genus.[32,33] Unlike antibiotics, Endobioma has little risk of developing resistance.[26] Resistance mechanisms such as active efflux from the cell or decreased membrane permeability are avoided due to the external application.[34] Moreover, *S. aureus* membrane peptidoglycans is a highly preserved structure, difficult to alter. Last, Endobioma-triggered cell wall destruction is independent of host metabolism, so there is no pressure for the bacteria to evolve.[27]

Our study adds new evidence to the potential and current trend to target the skin microbiome for AD management as we further understand the role of skin microbiome dysbiosis and *S. aureus* in its pathogenesis.[11] Though follow-up studies should be conducted to assess the effect of Endobioma on the skin microbiome composition, our results both show the rapid anti-*S. aureus* activity of the cream in vitro and its efficacy in managing AD in vivo.

The clinical improvements shown in this study confirm previous, preliminary case report of three cases of recurrent *S. aureus*-related dermatoses that were successfully treated with the endolysin-containing cream.[35] When used in a double-blind, vehicle-controlled study in conjunction with TCS, the endolysin-cream failed to demonstrate an effect on corticosteroid use (MAAS study).[35] However, prior to inclusion, patients were treated for 2 weeks with a moderate TCS dose, dramatically reducing their AD severity, and could continue using TCS with the endolysin-cream. Both factors could have contributed to masking the full benefit of endolysin vs vehicle. For those reasons and to really gauge the benefit of this new technology, we chose to use the Endobioma-containing cream as a monotherapy in patients with a higher initial SCORAD.

Of interest is the rapidity of the benefits observed with Endobioma. SCORAD was reduced by 43% after 7 days and 68% by 14 days. In a similar study design, the Eczema Area Severity Index (EASI) and the Atopic Dermatitis Severity Index (ADSI) were reduced by 51% and 54% after 2 weeks.[36] Although numerical improvement comparison is difficult with different scoring scales, our study showed an itch severity reduction of 74% at day 14 compared to 61% in the other study.

Poor adherence to AD treatment associated with side effects, treatment length or "corticophobia", is a known problem and can lead to *S. aureus* recolonization and flares.[37] Rapidly effective, TCS-free, with an inherent respect for the skin microbiota, and without observed side effects, Endobioma cream represents an attractive AD treatment solution. Additionally, our study highlighted a good cosmetic acceptability which may improve treatment compliance, potentially reducing flares. Interestingly, in the MAAS study[38] the number of doctor-reported flares was lower in the Endobioma group than in the vehicle group. Altogether, these results suggest that it would be worth assessing the long-term benefits of Endobioma as a proactive therapy to prevent and reduce the occurrence of flares and assess compliance.

CONCLUSION

This study showed that *S. aureus*-targeting Endobioma cream monotherapy produced a statistically and clinically significant reduction of AD severity scores and improved skin sensitivity and QoL in both adults and children. Safety and tolerability were excellent, enabling Endobioma to be applied to sensitive areas, thus, constituting a good option for AD patches in children. Future investigation assessing the *in vivo* effect of Endobioma-cream on the skin microbiome, particularly *S. aureus*, and immune response markers would be interesting to further understand the interplay between skin microbiome, skin immune response and AD clinical symptoms occurrence. Since Endobioma-cream is safe and offers an opportunity to prevent *S. aureus* over-colonization, it may be beneficial to prevent and reduce flares.

DISCLOSURES

Ann'Laure Demessant, Magali Moreau, Sophie Seité, Luc Aguilar, Olivier Da Cruz and Julia Puech are L'Oréal employees. Johan Frieling is a Micreos Human Health employee.

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ORIGINAL ARTICLE

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Safe Use of Adapalene 0.1 % Gel in a non-Prescription Environment

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ABSTRACT

Background: Topical retinoids are the mainstay of acne therapy and, until 2016, were only available by prescription. The margin of safety (MOS) of adapalene for potential teratogenic effects, and its use in pregnancy were investigated as part of the OTC switch.

Objective: To determine MOS using a maximal usage trial (MUsT) and animal embryo-fetal development studies. To conduct a thorough review of safety data with respect to use of Adapalene 0.1% Gel during pregnancy.

Methods: The MUsT was multicenter, open-label pharmacokinetic study which enrolled adolescents and adult subjects with mainly severe acne vulgaris. The no observable adverse event level (NOAEL) for adapalene teratogenicity was established in rat and rabbit embryo-fetal development studies. An exhaustive review of pregnancy data from multiple safety databases was conducted.

Results: The calculated MOS for teratogenicity was 70 for Adapalene 0.1% Gel. For the pregnancy safety review, no pregnancy malformations were attributable to topical adapalene use.

Limitations: Animal studies do not always predict effects in human development. Additionally, safety data is voluntarily reported and intrinsically incomplete.

Conclusion: Adapalene has a large and reassuring MOS making it suitable for OTC use. No teratogenic risk was identified in a MUsT and Pregnancy Safety Review. Adapalene 0.1% Gel is a safe and effective medication for the treatment of acne in a non-prescription environment. Based on available evidence, use of adapalene during pregnancy does not pose harm to the fetus.

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INTRODUCTION

Acne vulgaris is a condition that affects up to 87% of adolescents and over 50% of adults.[1] Acne sufferers commonly self-treat with well-established over the counter (OTC) products approved by the FDA under the OTC monograph. As a multi-factorial disease, acne is characterized by abnormal follicular keratinocyte desquamation, anaerobic *Propionibacterium acnes* proliferation, inflammation, and excess sebum production.[2]

Acne affects all races and ethnicities and is one of the most commonly diagnosed dermatological conditions. The prevalence of acne for women of childbearing age (19 to 45 years) is 32.5%, indicating potential for women who are pregnant to seek treatment.[3] Until 2016, there were five non-prescription active ingredients available on the market: benzoyl peroxide (BPO), salicylic acid, sulfur, resorcinol and resorcinol monoacetate. Topical retinoids have long been considered first line therapy for the treatment of acne.[4] The paradox is that some retinoids have a black box warning stating that women who are pregnant should not use these vitamin A receptor agonists.[5]

Excess systemic retinoid exposure during pregnancy can disrupt normal embryonic development in a wide range of experimental animals, targeting cardiovascular, CNS (central nervous system), craniofacial and skeletal development.[6] In humans, administration of systemic therapeutic retinoids has been associated with developmental abnormalities including CNS (hydrocephalus, hypoplastic or malformed cerebellar or cerebral cortices), craniofacial region (cleft palate, external ear defects), heart, thymus and limbs.[6] These abnormalities are associated specifically with oral retinoids. Although systemic exposure to topical retinoids is lower, the risk during pregnancy is inadequately studied.

Adapalene 0.1% Gel was originally approved as a prescription medication for the treatment of acne vulgaris in the United States in May 1996 (NDA 20380). Topical adapalene-containing products, formulated at various strengths between 0.1% and 0.3%, and in combination with BPO, were all approved Pregnancy Category C drugs before the FDA removed pregnancy categories from prescription medications.[7] This

further shows a distinct difference from oral retinoids based on the limited systemic exposure of the drug and properties of the molecule. Although adapalene is pharmacologically classified as a retinoid, it was engineered as a novel third-generation compound to provide clinical efficacy similar to tretinoin while minimizing cutaneous irritation.[8] More accurately, adapalene is a retinoid receptor agonist, as opposed to a true structural retinoid. Furthermore, adapalene is a synthetic polyaromatic compound that structurally differs from other retinoids due to the addition of the phenoxy adamantly substituent group.[9] This difference affects how adapalene interacts with retinoic acid receptors (RARs) and cellular retinoic acid binding protein-II (CRABP-II).[10,11]

Cellular retinoic acid binding protein-II (CRABP-II) is present in certain cells and helps facilitate the transfer of retinoids to the nucleus. Retinoic acid, tretinoin, and isotretinoin bind to CRABP-II and enter into the cell nucleus with high affinity.[12] Adapalene on the other hand binds to CRABP-II with very low affinity (> 1000nM).[9,12-14]

Compared with other therapeutic retinoids, adapalene has diminished access to the cell nucleus. This is important because tissues with CRABP-II are sensitive to high levels of retinoic acid which may cause defects in the development of those tissues.[14] Within the nucleus, adapalene exhibits selective high affinity binding for the nuclear retinoic acid receptors (RARs), RAR-β and RAR-γ but has a very low affinity for RAR-α; consequently, adapalene's ability to induce changes in gene expression also differs from other retinoids.[9] These differences in basic pharmacology suggest that adapalene effects after systemic exposure may be less as compared to other retinoids.

Adapalene was approved for OTC use on July 08, 2016 in the United States.[9] This was a first in class approval of an OTC topical retinoid for the treatment of acne. Like with all medications, women of childbearing age and pregnant women who use adapalene should be under the supervision of a physician to avoid potential misuse of the drug.[15] Pharmacokinetic studies were conducted as part of its original prescription approval.[16] However, technological advances have increased the sensitivity of detecting adapalene in plasma. As part of the OTC switch, a PK study was conducted under maximal use conditions, which included adolescents, to determine the exposure to adapalene using the latest methodologies.[17, 18] An exhaustive pregnancy safety review was also conducted to assess outcomes in pregnant women exposed to adapalene.

MATERIALS AND METHODS

Maximal Usage Pharmacokinetic Trial (MUsT)

The MUsT was conducted in 2014 in accordance with the Declaration of Helsinki, Good Clinical Practice, and other relevant regulatory guidelines. The study was designed according to the Food and Drug Administration (FDA) Guidance applicable at that time.[16] This study is considered as a Maximal Usage trial, ie, MUsT.[16,1,17,18]

Study Design

The MUsT was a PK, multicenter, randomized, open-label study conducted in 24 adult and adolescent patients with acne to assess adapalene plasma concentrations after repeated topical applications of Adapalene 0.1% Gel under maximal use conditions. The study was conducted in the USA (IND 116864).

Once-daily applications of Adapalene 0.1% Gel were administered for 29 days, by a qualified person at the study site, in a sufficient amount in order to leave a thin film of gel on all the area potentially affected by acne: face, shoulder, upper chest and upper back (ie, not only the affected area).

Bioanalysis/ PK/ Statistical Analysis

Plasma levels of adapalene were quantified using bioanalytical method with a lower limit of quantification of 0.02 ng/mL, ie, 5 time lower than that used previous PK Studies. Complete PK profiles were obtained at different study time periods (day 1, day 15 and day 29).

PK parameters (C_{max}, C_{trough}, T_{max} and $AUC_{0\text{-}24h}$) were calculated using a non-compartmental method (Phoenix® WinNonlin®, validated version 6.3, Certara L.P. Princeton, New Jersey, US).

PK parameters were analyzed descriptively using SAS® software using PROC MIXED procedure in SAS including the subject as a random effect factor and study visit (sampling day) as a fixed effect factor in the model (versions 9.2).

Safety Margin Calculation

Embryo fetal development studies were conducted in the rat and rabbit by both the oral and dermal routes to assess teratogenicity potential of adapalene. Oral studies performed either in the rat or the rabbit at high dose levels (up to 60 mg/kg/day). In dermal studies, gel formulations were used up to 0.3%, corresponding to 6 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) was defined as the highest dose at which no which adverse malformations were observed. The area under the curve ($AUC_{0\text{-}24h}$) was used to assess the extent of adapalene systemic exposure at the NOAEL doses. The animal species with the lowest $AUC_{0\text{-}24h}$ at NOAEL dose was defined as the most sensitive species. The safety margin (MOS) was calculated as the ratio of $AUC_{0\text{-}24h}$ in the most sensitive species at NOAEL dose to the highest human $AUC_{0\text{-}24h}$ determined in the MUsT.

Pregnancy Safety Review

A global safety review was conducted to identify pregnancy outcomes for pregnant women exposed to dermal adapalene during clinical trial and post marketing. The following databases were searched: Galderma's global pharmacovigilance database, FDA Adverse Event Reporting System (FAERS) database,

VigiBase (WHO database) and published literature. These cases were classified into retrospective and prospective cases and analyzed for pregnancy outcomes. The dates for the search were June 1st, 1996, the date of initial commercial launch of the product, through November 30, 2019.

RESULTS

Maximal Usage Trial

Subject Distribution

Subject demographics are summarized in Table 1. There was a similar distribution of males and female. A total of 24 subjects presenting mainly severe acne were enrolled in this study. The disease severity at baseline was moderate for 3 subjects (IGA = 3) and severe for 21 subjects (IGA =4)

Quantity of Product Used

The mean daily medication usage was 1.950 g/day overall at baseline ranging from 1.2 to 2.92 g/day. Overall, mean average daily medication (1.949 g/day) was nearly identical to the baseline dose indicating that the actual amount applied at subsequent visits was essentially the same as at initial visit as set in the protocol.

Pharmacokinetic Results

The plasma levels of adapalene were quantified at the first topical application (day 1), after 2 weeks (day 15), and at the end of the treatment period (day 29). (Figure 1, Table 2)

At the end of treatment period, adapalene plasma concentrations were quantifiable in all 24 subjects with concentrations ranging from 0.025 ng/mL to 0.171 ng/mL. The mean C_{max} was 0.049 ± 0.030 ng/mL and the mean $AUC_{0\text{-}24h}$ was 0.83 ± 0.49 ng.h/mL.

The time to maximum concentration (T_{max}) values remained constant throughout the study duration with median values of ranging from 12 hours to 14 hours.

There were no notable differences of adapalene mean plasma concentrations over visit days. This suggests that there was no accumulation upon repeated daily topical applications.

The most exposed subject was a 16-year-old male receiving daily application of 1.9 g of study medication on 1899 cm^2 skin surface area. This subject had quantifiable plasma levels of adapalene throughout the assessment period and presented the highest systemic exposure at day 29 with a C_{max} value of 0.171 ng/mL and an $AUC_{0\text{-}24h}$ of 2.90 ng.h/mL.

MOS Calculation

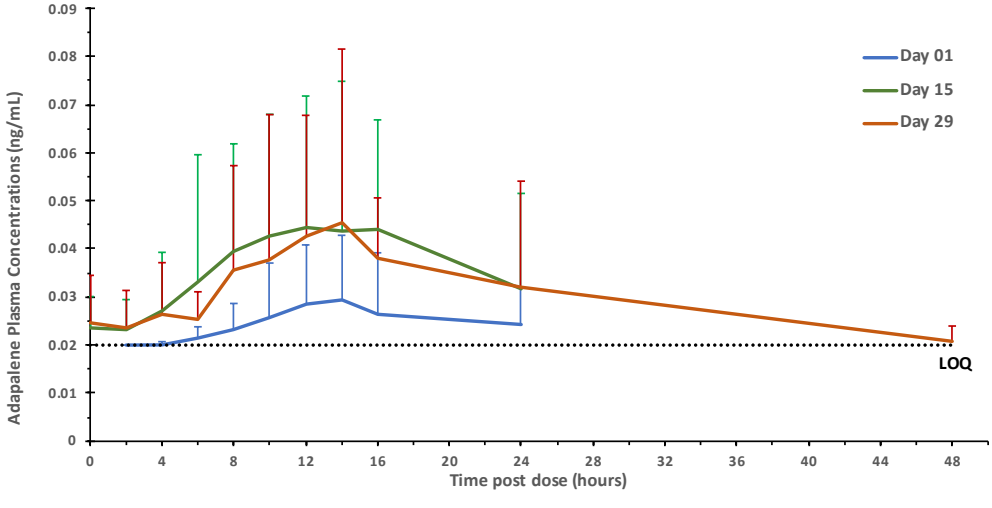
Adapalene induced teratogenicity (structural malformations) after oral administration at high systemic exposures (≥ 25 mg/kg/day), and 5 mg/kg/day was considered the NOAEL for effects on embryo-fetal development in both species.

By the dermal route, no fetal malformations were observed at doses up to the highest tested dose and the NOAEL was set at 6 mg/kg/day in rat and rabbit.[19] The plasma $AUC_{0\text{-}24h}$ at dermal NOAEL doses for embryo-fetal development were 204 ng.h/mL in rats and 1036 ng.h/mL in rabbit. When comparing the $AUC_{0\text{-}24h}$ exposures in rats (204 ng.h/mL) at the NOAEL to human maximal exposure ($AUC_{0\text{-}24h}$: 2.9 ng.h/mL), the calculated safety margin was 70 (Table 4).

Pregnancy Safety Review

A total of 332 cases of exposure to adapalene during pregnancy was identified: 56 cases from clinical trials and 276 from post-

FIGURE 1. Time profiles of adapalene plasma concentrations on day 1, day 15, and day 29/ET (Safety Population).



SD=standard deviation; LOQ: Limit of quantification (0.02ng /mL)
For graphical purpose, non-quantifiable individual concentrations of were imputed with the LOQ value (0.02 ng/mL)

TABLE 1.

Summary of TEAEs Through Week 8 (Safety Population; Pooled Data)

	Males (N=13)	Females (N=11)	12 to 17 years (N = 18)	18+ years (N= 6)	Total (N=24)
Age (years)					
Mean	18.8	17.4	15.5	26.2	18.2
Median (min, max)	16.0 (13, 43)	16.0 (14, 23)	16.0 (13, 17)	23.0 (18, 43)	16.0 (13, 43)
Gender					
Male	13 (100%)	NA	10 (55.6%)	3 (50.0%)	13 (54.2%)
Female	NA	11 (100%)	8 (44.4%)	3 (50.0%)	11 (45.8%)
IGA Score at Baseline					
3 = Moderate	0	3 (27.3%)	3 (16.7%)	0	3 (12.5%)
4 = Severe	13 (100.0%)	8 (72.7%)	15 (83.3%)	6 (100.0%)	21 (87.5%)
IGA Score at Baseline for 12 to 15 years					
3 = Moderate	0	3 (27.3%)	NA	NA	3 (12.5%)
4 = Severe	4 (30.8%)	1 (9.1%)	NA	NA	5 (20.8%)
IGA Score at Baseline for 16+ Years					
3 = Moderate	0	0	NA	NA	0
4 = Severe	9 (69.2%)	7 (63.6%)	NA	NA	16 (66.7%)

IGA: investigator global assessment, NA: not applicable

TABLE 2.

Summary of Pharmacokinetic Parameters

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)
Day 1 - N=24, N quantifiable (%): 15 (63%)			
Mean±SD	0.033±0.015	14.3±5.4	0.57±0.14
CV%	45%	38%	25%
Min, Max	<0.020, 0.066	8,24	0.48, 0.96
Median	0.031	14	0.52
Day 15- N=22, N quantifiable (%): 21 (95%)			
Mean±SD	0.054±0.032	12.8±5.3	0.87±0.43
CV%	59%	42%	50%
Min, Max	<0.020, 0.144	8, 24	0.48, 1.99
Median	0.044	12	0.73
Day 29- N=24, N quantifiable (%): 24 (100%)			
Mean±SD	0.049±0.030	11.9±4.5	0.83±0.49
CV%	62%	38%	59%
Min, Max	0.025, 0.171	0, 24	0.50, 2.90
Median	0.042	12	0.68

SD=standard deviation, CV: coefficient of variation, defined as the ratio of SD to arithmetic mean
For mean and median calculations, the following imputation rules were used for individual concentrations below the limit of quantification
- LOQ value (0.02 ng/mL) for C_{max}
- The lowest calculated value (i.e., 0.48 ng.h/mL) for AUC_{0-24h}
- No imputation for the mean calculation of T_{max}

TABLE 3.

Outcomes of Prospectively Identified Pregnancies

Pregnancy Outcome	Post-marketing Surveillance	Clinical Trials	Total	Rate (%)
Elective abortion	2	2	4	3.3
Miscarriage	4	3	7	5.7
Live births including	85	27	112	--
Healthy birth	83	26	109	--
Malformation	2	0	2	1.8
Other abnormal outcome (abruption placenta and fetal death)	0	1	1	0.8
Total	91	32	123	--

TABLE 4.

Safety Margin for Most Exposed Subject and Entire Study Population

	Human Exposure AUC_{0-24h} (ng.h/mL)	Rat Exposure AUC_{0-24h} (ng.h/mL)	Safety Margin
Most exposed subject	2.90	204	70
Average exposure	0.87	204	234

marketing reporting. After loss to follow-up and excluding cases that ended in voluntary termination from the study, 123 cases were identified (112 live births, 7 miscarriages, and 4 elective abortions). None of the observed malformations were consistent with retinoid teratogenicity indicating the birth defects were unrelated to adapalene use.

When pregnancy outcomes were analyzed from an epidemiological point of view, they were categorized as either prospective or retrospective cases. Prospective pregnancies were defined as being notified of drug exposure before the pregnancy outcome was known (including findings through prenatal diagnosis). Retrospective pregnancies were where the nature of the outcome motivated the case notification.

In total, there were 19 cases of abnormal pregnancy outcomes after maternal exposure to Adapalene. These were analyzed with respect to possible causal association between drug exposure and pregnancy outcome. The role of adapalene was considered questionable or was excluded. In some case other explanations were identified such as the type of anomaly observed was not consistent with retinoid deformations based on the time of exposure during pregnancy or the information was too scarce to lead to any conclusion.

Pregnancy outcomes can be interpreted from an epidemiological point of view only if the outcome was not known at the time of notification to the pharmacovigilance center, the pregnancy having occurred during clinical trials or not. Table 3 summarizes the 123 such pregnancies that were identified using these criteria.

DISCUSSION

Since oral retinoids can cause harm to the fetus if used during pregnancy, there has always been some uncertainty about using a topical retinoid.

The MUsT was specifically designed to evaluate the potential impact of the application of gel to a large surface area, as may be the case in clinical use by adults and adolescents without monitoring or direction from a healthcare provider. It was determined that Adapalene 0.1% Gel has a safety margin of 70, which indicates that systemic exposure to the drug is very low even under maximal use conditions. These data are particularly reassuring as the 3 subjects who applied the highest amounts of drug product daily (>2.5 g) to the highest surface areas (>2000 cm^2) did not have the highest systemic exposure to adapalene.

This large MOS represents a conservative estimate because it was calculated using the highest individual human exposure ($AUC_{0\text{-}24h}$: 2.9 ng.h/mL) instead of utilizing the mean value ($AUC_{0\text{-}24h}$: 0.87 ng.h/mL).

It is noteworthy that most consumers will use much less drug product than the amount used in MUsT (up to 2.92 g) providing even larger MOS. An actual use study conducted in 947 adolescent and adult subjects with self-reported acne demonstrated that 86% of the subjects used less than 1 g of Adapalene 0.1 % Gel, per day (daily mean use was 0.6 g per day).

Unlike oral or intravenous drugs, there is a finite amount of product that can be topically applied. To reduce the MOS to from 70 to 0, it would likely take the application of 4 (45 g) tubes per day. This equates to approximately a year's supply of typical use, which is virtually impossible to envisage. These data indicate that even if Adapalene 0.1% Gel is applied as needed ie, without restriction, systemic exposure to adapalene is consistently very low, and large margins of safety exist to ensure the safe use of adapalene in a nonprescription environment.

The rate of miscarriages, ie, 7 out of the 123 prospective cases with known outcomes (5.7%, Table 3) is lower than the expected range, (estimates vary from 14% to 19% in developed countries).[20] One fetal death (due to the abruption of placenta) corresponds to 0.8% of total known birth outcomes. This is lower than the rate of 3.4 to 9.9 per 1000 observed in Europe.[20, 21]

The rate of congenital structural malformations at birth in the general population is 2-4%.[10] The rate of malformations associated with adapalene, ie, 2 out of 112 cases full-term infants (1.8%, Table 3) is similar to the general population. As expected with the low systemic exposure to adapalene, no evidence for reproductive toxicity of adapalene was identified.

OTC use of drugs poses potential risks that must be weighed against the benefits. Overall, adapalene has been approved as a prescription drug in 83 countries in the world since 1994 including Canada, Japan, and Australia as well as most countries in Europe, Asia, and South America. Adapalene 0.1% Gel is available in the United States as an over-the-counter treatment of acne in patients 12 years of age and older since 2016. Adapalene 0.1% Gel is also approved in Russia where it has been available as a nonprescription drug since 2001. Extensive nonprescription experience in the United States and Russia, as well as the results of the MUsT described herein, and analysis of pregnancy exposures, is collectively supportive of the safety of Adapalene 0.1% Gel.

There have been no adequate and well-controlled studies of Adapalene 0.1% Gel in pregnant women. Health providers and women should make an informed decision together whether to use Adapalene 0.1% Gel or to stop and consider other treatment options when pregnant or planning to become pregnant. However, based on the available evidence, topical exposure to Adapalene 0.1% Gel during pregnancy, if exposure has occurred, does not cause birth defects in humans, and should reassure HCPs when counseling their patients.

DISCLOSURES

Dr. Weiss has served as a consultant/advisory board member, clinical investigator and speaker for Galderma Laboratories, Foamix, Almirall, and Ortho Dermatologics. Dr. Mallavalli was an employee of Galderma Laboratories, L.P. at the time of manuscript preparation. Dr. Meckfessel, Sean Griffin, and Nathalie Wagner are current employees of Galderma Laboratories, L.P.

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ORIGINAL ARTICLE

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The Efficacy and Safety of a Novel Protective Complex Combined With 50% Glycolic Acid Peel: A Double-Blinded, Split Face, Controlled Study

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ABSTRACT

Background: Glycolic acid (GA) is a commonly used superficial peel with higher concentrations and lower pH levels leading to a stronger effect despite a higher risk of adverse effects (AE), which include burning, pain, itching, erythema, and edema.

Objective: This study aimed to evaluate the potential of a novel protective complex (NPC) to reduce facial AEs following a GA chemical peel treatment.

Methods and Materials: Twenty volunteers were selected for the study. A pair of numbered kits were supplied by and randomly assigned to be applied to each side of a patient's face with either a 50% GA peel plus NPC or a control formulation with only a 50% GA peel. AEs, patient photographs, and standard and red filtered VISIA scans were evaluated by three independent dermatologists.

Results: The average post-treatment pain and itching were significantly higher in the control half as compared to the study half. Recovery time appeared to be significantly shorter in the treated side compared to the control side.

Conclusion: The addition of the NPC to GA 50% peel is a highly effective, safe modality in the reduction of erythema, pain, and itching after peel application, and it provides an advantage in the post-treatment healing period.

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INTRODUCTION

Chemical peels are a popular, effective, noninvasive and relatively safe modality to improve skin appearance and to treat various skin problems, such as acne, pigmentation, scars, wrinkles, melasma, and photoaging among others. They are categorized according to their depth of penetration into superficial, medium, and deep peels.[1,2] Peels are commonly used in clinical settings and found in many cosmetic products.[1,3]

Glycolic acid (GA) is a commonly used superficial peel with higher concentrations and lower pH levels leading to a stronger effect despite a higher risk of adverse effects. Most common adverse effects following glycolic acid peel are the sensation of burning, pain or itching, erythema, and edema.[1,3-5] A novel protective complex (NOON Aesthetics®, Tel Aviv, IL), known as the DermShield™, was developed to be added to the peel in order to allow the use of high concentration GA peel at a low pH, while reducing the accompanying negative adverse effects on the skin. The purpose of this study is to examine this novel protective complex (NPC) for its anti-irritation effect, tolerability, efficacy, and safety while added to the GA 50% peel.

MATERIALS AND METHODS

This prospective, double blind, split-face controlled study aimed to evaluate the potential of the NPC to reduce facial adverse effects following a GA chemical peel treatment. The clinical trial was carried out at an outpatient private clinic in the period from January 2019 till March 2019. After approval of the Institutional Review Board (IRB), informed consent was obtained from all subjects prior to beginning the study.

One month prior to the trial, all patients could apply only a moisturizer and a sunscreen. A pair of numbered kits were supplied by NOON Aesthetics and assigned to each patient. The company used a designated software to randomize the patient number, facial halves, and the treated (50% GA peel plus NPC) Vs. the control formulations (only 50% GA peel). The two kits were identical in shape, size, and weight, as well as color, odor, and consistency. A randomized list was kept away to ensure the integrity of the trial. Neither the treating physician nor the patients knew which facial half was treated by the study or control kit.

Demographics, including age, medical history, dermatological

history, smoking, drugs, alcohol use, and skin type were collected before enrollment to the study. Excluded patients had cut or broken skin, known active or chronic skin disease, a personal history of abnormal bleeding, scarring, or wound healing. Patients were also excluded if they were pregnant or breastfeeding, reported known hypersensitivities to glycolic acid or other alpha-hydroxy acid (AHA) peels/products, or had a prior medium or deep chemical peel, prior laser treatment, fillers, or botulinum toxin facial procedures within three months of enrollment. Additional exclusion criteria included the use of retinoids, immunosuppressive drugs (steroids, NSAIDs, chemotherapeutic, biological agents), or photosensitizing medications in the past 6 months.

Prior to treatment, the subject's skin was cleaned using a mixture of 50% alcohol and 50% acetone. The peels were applied by a licensed nurse with experience using AHA peels under medical supervision. Two ml of the NOON Aesthetics Peel Formula containing 50% glycolic acid peel and 0.9 pH with the NPC were applied to half of the subject's face (treated side), while two ml of the NOON Aesthetics Peel Formula containing only 50% glycolic acid peel, 0.9 pH without the protective complex was applied to the other half (control side). After a 15-minute application, the GA peel was then neutralized with a formula containing sodium bicarbonate on both sides.

Subjects were photographed before and at 3-, 15-, and 30-minutes post-peel application, as well as 120 minutes following peel neutralization. Evaluation of the standard and red filtered VISIA (Canfield Scientific, Parsippany, NJ) photographs was performed by three independent dermatologists using the following scale: 0–no difference between the two halves of face, 1–minimal difference (1–25%), 2–mild difference (26%–50%), 3–moderate difference (51%–75%), 4–significant difference (76%–100%). Erythema was also measured at each time point by a MX18 Mexameter® (CK Electronic GmbH, Cologne, Germany).

Pain and itching at both halves over time were evaluated using a standard numerical 10-point Visual Analogue Scale (VAS). Subjects were asked to mark the scale according to their assessment of pain and sensory irritation as experienced at a given time point, from 0 (no pain/sensory irritation) to 10 (worst possible pain/sensory irritation). At follow-up visit, subjects were requested to evaluate healing time by indicating the time frame (in hours) needed to reach full resolution of the following parameters: edema, redness, and sensation of heat and time to return to normal daily activity.

Following the peel, subjects were instructed to apply sunscreen SPF 30 or higher, avoid any exposure to the sun, and report to the clinic about any type of serious adverse events.

Analyses were carried out using SPSS 25.0. The Wilcoxon paired t-test was used for comparing the treated and non-treated sides. Friedman's test was used to compare the changes in erythema changes over time followed by Dunn's post hoc test. *P* values <0.05 were considered statistically significant.

RESULTS

From the pool of potentially eligible patients, 20 healthy female volunteers between the ages 40 and 54 (mean: 45.5 ± 4.6) were selected for the study. Most subjects (n=19) were classified as Fitzpatrick skin type II or III. One subject was classified as Fitzpatrick skin type I. No background diseases were reported except for one subject who suffered from atopic dermatitis. All subjects completed the trial. When evaluated by three independent dermatologists for erythema, all raters observed no significant difference in erythema between the two sides of the face at baseline and in the last follow-up visit. However, a significant reduced level of erythema on the treated side at 3-, 15-, 30-, and 120-minutes post-treatment were scored by all raters. A representative patient is seen in Figure 1. The three raters' erythema score differences between the treated and control sides over time are shown in Figure 2.

At baseline, the objective measured levels of erythema taken with Mexameter technology were 364.2 and 354.35 for the treated and control sides respectively. After 3 minutes, the control side experienced a jump in erythema to 486, then a steady decrease to 369.65 after 120 minutes. The treated side

FIGURE 1. Representative patient over time. Right half – control, left half – treated with the novel protective complex (DermShield™).

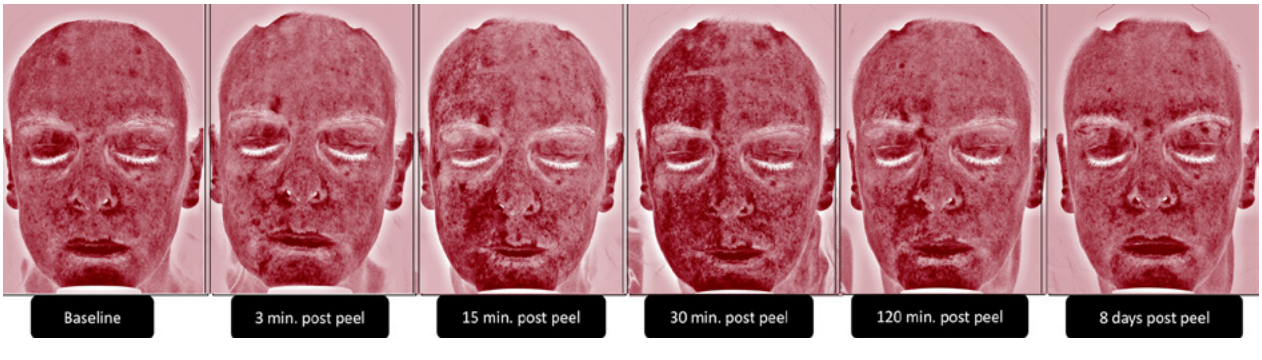

FIGURE 2. Erythema score by raters over time. Insignificant differences between treated and control sides were evaluated by the raters at baseline and follow-up observations. Significant differences between study and treated sides were scored by all raters at 15 minutes, 30 minutes, and 2 hours post-peel (*P*<0.001).

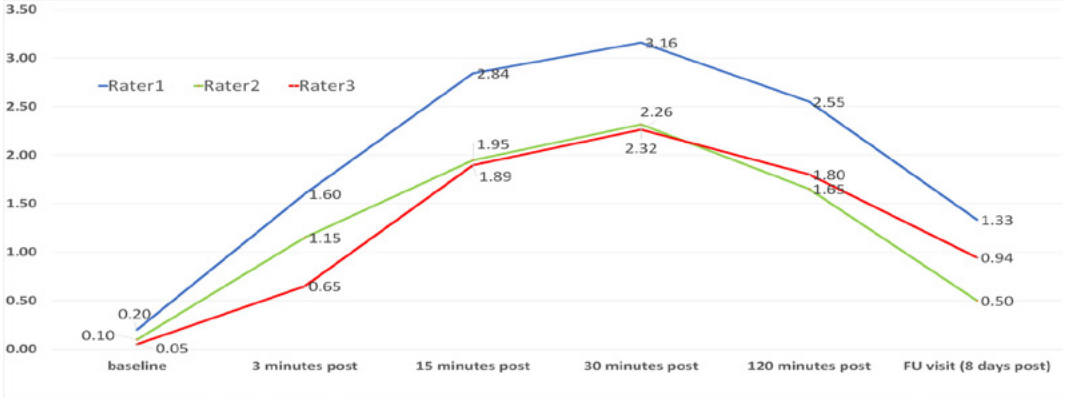

TABLE 1.

Time of Resolution (in hours) of Treated Versus Control Side								
	Edema		Redness		Post Treatment Recovery Time		Hispanic/Latino[a]	
	Treated	Control	Treated	Control	Treated	Control	Treated	Control
Mean (sd)	8.4 (16.1)	47.4 (60.1)	24.0 (29.9)	57.1 (42.7)	9.7 (16.3)	42.1 (61.3)	4.1 (8.7)	27.2 (32.4)
P value	0.006		0.016		0.030		0.012	

experienced a jump in erythema to 381.0 after 3 minutes. Then a decrease in erythema to sub-baseline levels was observed with Mexameter at 351.65 after 120 minutes. At 30 minutes, mean erythema score was significantly higher on the control side in comparison to the treated side (453.6 ± 55.2 vs 359.8 ± 58.1, *P*-value =0.008)

The average pain and itching, at 3-, 15-, 30-, and 120-minutes post treatment were significantly higher in the control half as compared to the study half. On the treated side, itching and pain were rated using the VAS as 1.15 and 2.0, respectively, at 3 minutes after application, steadily decreasing to 0.15 and 0.10 after 120 minutes. The control side was subject to itching and pain rated as 5.05 and 6.50, respectively, 3 minutes after application, and remained at 0.45 and 1.35, respectively, after 120 minutes.

Post treatment recovery time (till full resolution of facial redness, edema, heat sensation) as well as time to return to normal daily activity appeared to be significantly shorter in the treated side compared to the control side (Table 1). More reported AE with mild to moderate severities were reported in the control halves, which included acne, sensation of burning, erythema, rash, itching, and dryness for an average of 3.89 days (range, 2 to 8 days).

DISCUSSION

Chemical peels are an effective, noninvasive, and relatively safe modality to improve skin texture and tone and to treat various skin problems, such as acne, pigmentation, scars, wrinkles, melasma, and photoaging among others. They are widely used in clinical settings and found in many cosmetic and medical products. By using caustic agents targeted to a specific cutaneous depth, controlled injury and inflammation lead to a process of normal wound healing and rejuvenation as well as thickening of the epidermis.[1,3] The different peels are categorized according to their depth of penetration into superficial, medium, and deep peels.[1,2,6]

GA is a commonly used type of (AHA) normally applied in concentrations ranging from 20%–70% and pH levels of 0.08–2.75 in non-buffered solutions. GA peels are generally considered superficial peels and usually require neutralization in order to cease further acidification of the skin, after which a transient burning or pain sensation followed by erythema and edema are expected.[1,3,4] Potential effects can be altered by the peel's concentration, pH level, number of applied layers, and exposure time. Both concentration and pH levels play important roles in establishing the potency of GA peels with evidence pointing to pH levels being more dominant. Lower pH levels lead to a stronger effect despite a prolonged healing time and higher risk of complications.[1,2,5] which includes amongst other allergic reactions blistering, folliculitis, acne outbreaks, infections, herpes recurrence, ecchymosis secondary to edema, hypopigmentation as well as hyperpigmentation, textural cutaneous changes, and scarring. These complications can occur immediately or within a few days to weeks after the treatment.[7-10]

In an attempt to reduce the negative adverse effects and possible complications, several strategies are employed. Strontium salts

were reported to have inhibitory properties in the processes of irritation sensation and inflammation while maintaining the AHA efficacy without the side effects of local anesthetic in topically applied solutions. The mechanism for strontium's inhibitory effect is unclear, however, a possible explanation is that strontium may have a direct effect on signal transmission via nociceptor C fibers.[11-14] Methyl-sulfonyl-methane (MSM) is an organic sulfur rich compound found normally in our diet attributed to have anti-inflammatory properties.[15] It has been tested in treating various conditions such as rosacea, musculoskeletal disorders, and hemorrhoids and can be administered topically and orally.[16-19] The breakthrough technology of the NPC combines strontium and MSM in a patented formulation, creating a synergistic effect most useful in decreasing the development, incidence, and severity of skin irritation and erythema related to the peel, thus enabling the use of high concentration active ingredients in topically applied cosmetics and achieving desired results while reducing the accompanying unpleasant sensations.

This current study examines the NOON Aesthetics NPC while added to GA 50% peel. Our study demonstrated that the addition of the NPC to GA 50% significantly reduces the post-peel erythema, itching, and pain compared with the side treated with 50% GA alone. This effect was clearly observed within the first few minutes after peel application, lasting for at least two hours post treatment. In addition, the post-peel adverse effects were mild to moderate and appeared to be less prevalent on the side treated with 50% GA plus NPC. Neither the patient nor the evaluating physicians noted any difference in the final post-peel cosmesis at the follow-up visit.

Despite the use of the NPC, efficacy of the GA treatment was not compromised and observed to be the same across the treatment and control groups. While local irritation is an indication of the effect of GA, it is a side effect of the peel, and the efficacy is a parameter of the pH of the formula, the concentration of the acid, and the application time, which were maintained across the treatment and control groups.

LIMITATIONS

Limitations of our study included a relatively small study size of 20 individuals and limited testing to mostly Fitzpatrick skin types II and III. The NPC was tested only with formulations of highly concentrated GA, whereas other chemical peels at different concentrations were not tested. It is also difficult to truly assess the clinical improvement of both sides after only a single GA 50% peel. Furthermore, we did not follow up with patients on the long-term efficacy of the peel with the NPC.

Future directions should evaluate the true utility of NPC with respect to other AHA and beta-hydroxy acid formulations on different skin types and using multiple treatments. Additionally, further studies with larger cohorts are needed to establish the NPC as a safe and effective standard clinical product. Additionally, long-term split-face objective studies are needed to compare the efficacy of a peel with the NPC to a peel without the NPC.

CONCLUSION

In conclusion, the addition of NPC to GA 50% peel is a highly effective, safe modality in the reduction of erythema, pain, and itching sensation after peel application, and it provides an advantage in the post-treatment healing period.

DISCLOSURES

The study was sponsored by NOON Aesthetics®, Tel Aviv, IL.

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CASE REPORT

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Chromate-Induced Allergic Contact Dermatitis Treated With Dupilumab

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ABSTRACT

Chromate causes persistent, difficult to treat irritant and allergic contact dermatitis in cement-handling occupational workers. When therapeutics such as topical corticosteroids, topical calcineurin inhibitors, phototherapy and immune-modulating treatments like methotrexate fail, many patients are advised that avoidance may be the only remaining option – an option that may be particularly challenging if the patient's occupation necessitates chromate exposure. We report a case of severe chromate-induced allergic contact dermatitis in a 55-year-old cement mason that presented to the outpatient dermatology clinic with multiple scaly, erythematous, >5 cm plaques scattered over the skin of his hands, head and neck. After a prior failed course of treatment with high potency topical corticosteroid, this patient was successfully treated with dupilumab. Given the success of dupilumab in our patient, we propose the consideration of dupilumab as an alternative treatment option for those suffering from chromate-induced allergic contact dermatitis that is refractory to ultra-high potency topical corticosteroids.

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INTRODUCTION

Chromate, an anion of chromium and oxygen discovered by Vaquelin in 1798, is a common cause of occupational skin disease.[1] The prevalence of chromium sensitivity in the general U.S. population ranges from 0.08 to 7%.[2] Chromium can cause both irritant contact dermatitis and, more frequently, allergic contact dermatitis (ACD).[3] Nickel(II) ion is the most frequent cause of type IV hypersensitivity reactions, accounting for 23% of all cases diagnosed by patch testing, followed by cobalt(II) ion (9.3%) and hexavalent chromium (chromium[VI]) (5.6%).[4] Chromate is frequently used in plating, leather tanning, pigmentation, dye production, and chemical industries, and is found in cement as a byproduct of the cement manufacturing process.[5] Approximately one-third of bricklayers and stonemasons who are in frequent contact with cement, as well as one in ten metal operators who have an occupational disorder, received a diagnosis of contact dermatitis due to hexavalent chromium exposure.[4,6,7]

CASE

A 55-year-old Hispanic male patient presented to the outpatient dermatology clinic in October 2018 with intractable dermatitis. Scaly, erythematous, >5 cm plaques were present on the exposed skin of his hands, head and neck (Figure 1). Areas covered by clothing generally showed no lesions. History revealed that the patient worked as a cement mason, and the areas with the aforementioned skin findings were present only at the areas exposed to cement dust. The patient reported little to no improvement in the past with ultra-high potency topical corticosteroids.

FIGURE 1. Scaly, erythematous, >5 cm plaques are present on the exposed skin of the patient's hands.

The patient's past medical history was significant for bronchitis, a congenitally missing kidney, and hepatitis C infection that was successfully treated with anti-viral therapy. Past surgical history was significant for a left lung lobectomy secondary to bronchitis. The patient denied any concurrent medications other than topical corticosteroids. A 12-point review of systems was positive for bronchitis, chronic intermittent cough for which he is followed by his pulmonologist and primary care physician, and hypertension. A skin biopsy was performed at his right ventral forearm, revealing scattered melanophages with superficial perivascular and interstitial lymphocytic infiltrate, consistent with a diagnosis of contact dermatitis (Figures 2-3).

FIGURE 2. Low power photomicrograph of the patient's biopsy from the right ventral forearm. There are spongiotic vesicles in the epidermis and a superficial mononuclear perivascular infiltrate (4x magnification).

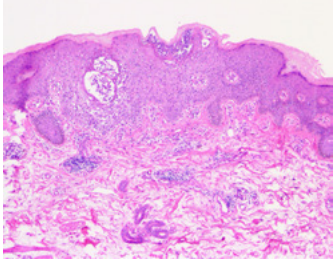
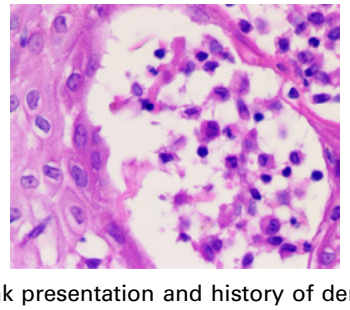


FIGURE 3. High power photomicrograph of the spongiotic vesicles. The spongiotic vesicles in the epidermis contain mononuclear cells (40x magnification).



Given the frank presentation and history of dermatitis only in areas where the patient was exposed to cement dust, the patient was not patch tested for chromium. Because he had not shown any clinical improvement in the past with ultra-high potency topical steroids, topical therapy was not reattempted. Due to his past history of viral hepatitis, methotrexate was considered but ultimately not pursued as a treatment option. Consequently, the patient was started on dupilumab, and received one loading dose of 600 mg. After a misinterpretation of the recommended dosing, the patient continued the 600 mg dose every two weeks for 2 months, at which time he presented for a follow up visit at which his dupilumab dose was decreased to 300 mg every two weeks. At that point, the patient's dermatitis had completely resolved (Figure 4), and he reported no adverse events (and, in particular, no conjunctivitis) throughout the treatment course. Though the patient's occupational exposure to chromate as a cement mason did not change, the patient's dermatitis remained clear for the next 18 months to date (July 2020).

FIGURE 4. Complete resolution of the patient's hand lesions following one year of treatment with dupilumab.

DISCUSSION

Clinically, chromate allergy appears as a severe, sometimes widespread, very persistent dermatitis, and is considered to have a relatively poor prognosis, often with therapeutic recalcitrance.[7] Commonly used treatments for chromate induced ACD include emollients, topical corticosteroids, and topical calcineurin inhibitors.

Treatments for persistent or severe chromate-induced contact dermatitis include phototherapy and immune-modulating treatments such as azathioprine, cyclosporin and methotrexate. Until recently, when these options failed, avoidance was the only long-term management strategy available, often with negative ramifications on the livelihoods of patients who are occupationally exposed to chromate.

The case we present provides a novel treatment approach for a rare form of ACD that has the ability to significantly impact the quality of life of those affected. Dupilumab is commonly used in the treatment of atopic dermatitis (AD), a helper T-cell 2 (TH2) axis-predominant immune disorder. Dupilumab acts as an IL-4 receptor antagonist and prevents the IL-4 and IL-13-mediated inflammatory responses seen in AD. Although ACD is considered predominantly a helper T-cell 1 (TH1)-mediated process, certain allergens sensitize via the induction of the TH2 pathways.[8,9] Dupilumab may be effective in the inhibition of allergens that elicit a TH2-mediated, IL-4 dependent ACD.[8] The ability of dupilumab to treat chromate-induced ACD in our patient also suggests that IL-4 or IL-13 may play a role in ACD. The role of IL-4 in ACD was confirmed in IL-4 knockout mice, which still have the ability to elicit contact sensitivities to oxazolone but not 2,4,6-trinitrochlorobenzene, a contact allergen with a TH2-mediated sensitization pathway.[8,10] Dupilumab may be an alternative treatment option for those suffering from chromium-induced ACD that is recalcitrant to even ultra-high potency topical corticosteroids.

DISCLOSURES

Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment.

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CASE REPORT

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Delayed Metastatic Polypoid Nodular Melanoma Diagnosis During COVID-19 Pandemic, Successful Treatment With Surgery and Nivolumab

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ABSTRACT

Patients with polypoid (pedunculated) melanoma have the poorest 5-year survival rate compared with all other variants of nodular melanoma, presenting with increased thickness, incidence of metastasis, and rates of ulceration. There are few published reports regarding the pathogenesis and treatment of polypoid melanomas. We report the successful treatment of a rapidly developing red nodular polypoid melanoma with metastasis using surgery followed by anti-PD-1 antibody nivolumab in a SARS-CoV-2-positive patient who delayed seeking care due to the COVID-19 pandemic.

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INTRODUCTION

Among the major subtypes of melanoma, nodular melanoma is associated with the poorest prognosis.[1] Nodular melanoma can be further subdivided into distinct variants, among which the polypoid (pedunculated) tumor has the poorest 5-year survival rate.[1,2] Polypoid melanomas are characterized by an aggressive vertical growth phase and have been associated with early metastases through invasion of blood and lymphatic vessels at the tumor's periphery.[3] Clinically, the polypoid variant has a cauliflower-shaped appearance, with the bulk of the lesion located above the epidermis.[1] Compared to other variants of nodular melanoma, polypoid melanoma is associated with younger age at presentation, increased thickness, more frequent ulceration, and higher probability of occult metastasis.[1]

Although surgical excision is the cornerstone of melanoma management, treatment of polypoid melanoma is complicated by several negative prognostic factors, including early metastasis.[4] Nivolumab, an anti-programmed-death-1 (PD-1) antibody, was approved for the treatment of unresectable or metastatic melanoma in 2014, but its role in the treatment of polypoid melanoma with metastasis is unclear.[5,6] We report the successful treatment of a rapidly developing red nodular polypoid melanoma with metastasis using surgery followed by nivolumab in a SARS-CoV-2-positive patient who delayed seeking care due to the COVID-19 pandemic.

CASE

We report the case of a 74-year-old man with rapid development of a forearm polypoid melanoma and metastasis concomitant with SARS-CoV-2 infection. An asymptomatic flat "sun spot" on the left forearm was noted by the patient approximately 6 months before diagnosis. It developed into an elevated 3.5 cm x 2.5 cm reddish skin nodule in the two months following SARS-CoV-2 infection. The patient had positive SARS-CoV-2 virus nasopharyngeal swabs and antibodies, in addition to multiple comorbidities including chronic obstructive pulmonary disease, diabetes, hypertension, hyperlipidemia, and atrial fibrillation. The patient delayed seeking care for the forearm tumor due to COVID-19, despite noticing the fast enlargement of the lesion into a large, bleeding nodule (Figure 1).

FIGURE 1. 3.5 x 2.5 cm nodular polypoid melanoma. Orange circle surrounds local metastatic lesion.

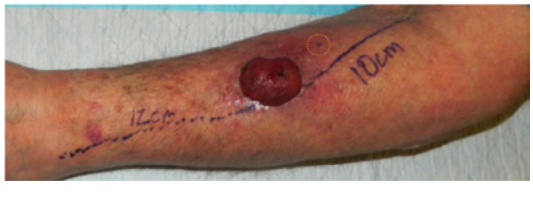


FIGURE 2. H+E staining demonstrating polypoid melanoma.

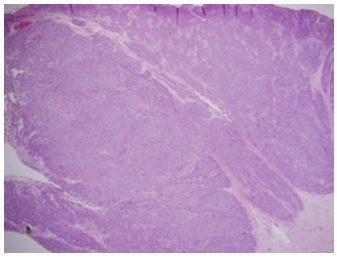
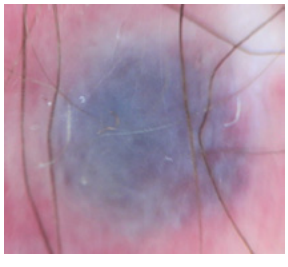


FIGURE 3. Dermoscopy view of local metastatic lesion.



Clinical and pathologic examinations were consistent with an ulcerated polypoid nodular melanoma (Figure 2) with satellite (Figure 3) and in-transit metastasis, which were excised with a 2 cm margin. The tumor cells were S-100 and Melan-A positive. BRAF V600 mutations were not detected. PET-CT scan showed hypermetabolic left axillary nodules, with the largest measuring 2 x 2.9 cm and 2.3 x 3.1 cm.

Treatment with anti-PD-1 antibody, nivolumab (Bristol-Myers Squibb), was initiated and well-tolerated by the patient. Adjuvant immunotherapy sessions were arranged for a duration of one year. Surgical removal of left axillary lymph nodes confirmed the diagnosis of Stage IV melanoma with oligometastatic disease of the axillary lymph nodes. The excision of the left axillary lymph nodes after 4 cycles of nivolumab given every 2 weeks at 240 mg showed 80% of a 2 cm lymph node and 90% of a 1.8 cm node replaced by necrotic melanoma. Over one-year post-diagnosis the patient is doing well after 20 cycles of nivolumab, with no reported adverse effects, well-healed surgical scars, and no recurrence.

DISCUSSION

Polypoid Melanoma Development in the Setting of SARS-CoV-2 Infection

Herein we present a case of polyploid melanoma that developed in the setting of SARS-CoV-2 with delayed presentation due to the COVID-19 pandemic, successfully treated with surgery and nivolumab. Polypoid melanoma pathogenesis has been associated with diminished immune response, as most cases of polypoid melanoma examined by Manci et al were not observed to have strong lymphocytic infiltration of the adjacent stroma.[1] It is possible that the immunosuppressive effects of SARS-CoV-2 contributed to the rapid progression of polypoid melanoma in our case. Persistent adaptive immune activation leading to lymphocyte exhaustion has been described in cases of chronic infections, tumorigenesis, and viruses.[7] In those with COVID-19, the reduction and functional exhaustion of cytotoxic T lymphocytes and natural killer cells have been reported.[7,8] Compared to healthy controls, SARS-CoV-2 infection results in significantly higher levels of exhaustion marker PD-1.[7,8] This is particularly relevant to melanoma, as PD-1 overexpression has been shown to promote melanoma tumor growth.[9] Thus, the immune effects of SARS-CoV-2 may have promoted the aggressive melanoma progression observed in our case.

Importance of Timely Melanoma Diagnosis and Treatment During the COVID-19 Pandemic

This case highlights the complex challenges of providing timely melanoma diagnosis and treatment during the COVID-19 pandemic. Early detection is essential to successful melanoma management, yet many outpatient visits have been postponed during the pandemic.[10] Postponing appointments can have lethal consequences as aggressive polypoid melanomas developing within a few months have been documented.[11] Further, red melanomas represent 72% of amelanotic melanomas, yet are frequently misdiagnosed as they are often confused with benign conditions such as pyogenic granuloma and dermatofibroma.[12] Our patient delayed seeking care due to COVID-19, even after noticing rapid progression of the flat lesion into a bleeding, elevated nodule (Figure 1). After presentation, the patient was referred to dermatology services due to unremitting bleeding.

Skin lesions displaying signs of aggressive skin cancers should be promptly referred for dermatologist evaluation. Referral for initial examination via teledermatology may be useful, although in practice there are limitations to virtual examination of pigmented lesions.[13] Even during pandemics, timely management of melanoma is necessary to avoid serious consequences, including metastasis, increased morbidity, and death.

Polypoid Melanoma Treatment in the Setting of SARS-CoV-2 With Surgery and Anti-PD-1 Therapy

Treatment for polypoid melanoma is surgical, but the incidence of metastasis at presentation is not uncommon and requires additional management.[1,4] The role of anti-PD-1 antibodies in the treatment of polypoid melanoma with metastasis is unknown.[5] A recent consensus guideline for melanoma management suggested that a single agent PD-1 inhibitor can be considered first-line treatment for metastatic melanoma during the COVID-19 pandemic.[14] In our case, lymph node removal after 4 cycles of nivolumab revealed that the two largest lymph nodes were replaced with necrotic melanoma by more than 80%. After 20 cycles of well-tolerated nivolumab therapy, the patient is doing well over one year post-excision. These observations suggest that in cases of red and polypoid

melanoma with metastasis, anti-PD-1 therapy can successfully supplement surgical removal. Studies confirming the efficacy of this combination approach are needed.

CONCLUSION

Our report details the rapid development of an aggressive polypoid melanoma with metastasis following infection with SARS-CoV-2 in a patient who delayed seeking care due to COVID-19. The polypoid melanoma was successfully treated with surgical excision followed by nivolumab and lymph node resection. The combination of surgery and adjuvant nivolumab should be further studied to determine its efficacy in treating polypoid melanoma with metastasis. The complex effects of COVID-19 on the development and management of melanoma must also be carefully examined. Delays in detection, diagnosis, and care of aggressive skin cancers during the pandemic may have potentially lethal consequences.

DISCLOSURES

The authors have no relevant conflicts of interest to declare.

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CASE REPORT

Journal of Drugs in Dermatology

Proliferating Pilar Tumor: Two Cases and a Review of the Literature

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INTRODUCTION

Trichilemmal cysts (TCs) are the most common cystic lesions arising on the scalp and up to 2% give rise to a proliferating trichilemmal tumor (PTT). A rare subset of PTTs are termed malignant due to their histologic characteristics, aggressive behavior and potential for metastasis.[1-3] The histological hallmark of TCs and PTTs is the absence of a granular layer resulting in abrupt trichilemmal keritanization.[1,3] PTTs are differentiated from TCs by the epithelial proliferation which shows anastomosing bands and trabeculae and occasionally mild cellular atypia.[1,3] Notably, PTT can resemble squamous cell carcinoma (SCC) histologically, however they can be differentiated as PTTs generally have abrupt keratinization, clear glycogen storage cells and sharp demarcation from the surrounding tissue without infiltration or replacement of adjacent structures. Immunohistochemical staining can also be used to differentiate SCC from PTT.[1,3-5]

Wide local excision (WLE) is the standard of care for PTT, however the recurrence rate is 3.7% on the scalp and 6.6% elsewhere on the body.[1] Additionally, rates of metastasis to lymph nodes have been reported as 1.2% from the scalp and 2.6% from other parts of the body.[5] The risk of malignancy within PTTs necessitates complete removal of the tumor.[5,6,8-11] Management guidelines for PTT were published by Satyaprakash et al in 2007 and here we describe 2 additional cases of PTT treated with Mohs micrographic surgery (MMS) and provide an updated review of the literature.[1]

METHODS

We included all cases of PTT reported in the English language literature from 1/1/2007 to 5/31/2020 that were confirmed via histology and did not appear to have been reported elsewhere following the publication of Satyaprakash et al review in 2007. This time frame was selected to build upon the literature review published by Satyaprakash et al in 2007. The PubMed and Cochrane databases were searched using the terms: "proliferating trichilemmal tumor," "proliferating pilar tumor," "proliferating pilar cyst," "subepidermal acanthoma," "invasive hair matrix tumor," "invasive pilomatrixoma," "trichochlamydocarcinoma," "hydatidiform keratinous cyst," "giant hair matrix tumor," and "trichochlamydoacanthoma."

CASE REPORTS

Patient 1

A 46-year-old woman with no significant medical history presented for re-excision of a PTT of the occipital scalp which was incompletely excised by an outside provider. Patient stated that it had been present for months, slowly enlarging and asymptomatic. Histology showed: "Proliferating follicular cystic neoplasm (proliferating trichilemmal cyst), fragmented. Note: Some authors consider this lesion to be a low-grade squamous cell carcinoma." After discussion with the pathologist and patient, we elected to perform MMS to ensure complete removal and optimize cosmesis.

The pre-operative lesion measured 2.5 x 2.3 cm. Clearance of the tumor required 4 stages of MMS with depth of invasion to just above the galea. The resultant surgical defect was 2.7 x 5.5 cm and this was closed primarily. The patient was noted to be free of any recurrence at a visit 2 months following surgery and during a telemedicine visit 13 months following surgery.

Patient 2

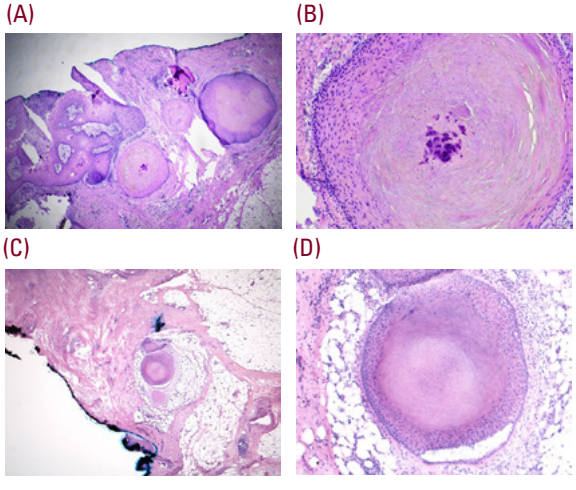
A 54-year-old woman with no significant medical history presented to our clinic for re-excision of a PTT of the left temporal scalp which was incompletely excised by an outside provider. Patient stated that the lesion had been present for over a year and had been enlarging and tender to palpation. Histology showed: "Fragments of proliferating follicular cystic neoplasm (proliferating trichilemmal/pilar cyst), probable." MMS was used for the same reasons mentioned above.

The pre-operative lesion size was 2.2 x 1.4 cm; the tumor was cleared with 2 stages of MMS showing invasion to the subcutaneous fat. The resultant defect measured 2.6 x 1.9 cm and was closed primarily. The patient was noted to be free of any recurrence at 2 months and during a telemedicine visit 11 months following surgery.

RESULTS

A total of 11 cases of PTT have been reported since Satyaprakash et al.'s 2007 review of the literature, including our own (Table 1). Our search showed that 7 of 11 cases (63.6%) were treated with MMS, three were treated with WLE, and one was treated

FIGURE 1. Frozen section histology from Mohs micrographic surgery, Patient 1 – (A) 4x view showing three cystic structures, all with isthmic lined epithelium. The cystic structure on the right demonstrates hyperplastic changes. (B) 20x view of the cystic structure lined by hyperplastic isthmic epithelium, with "classic" trichilemmal keratinization and central calcification. Note the lack of a granular layer. Patient 2 – (C) 2x view of three subcutaneous based cystic structures with trichilemmal-like central keratinization. (D) 10x view of a cystic structure lined by hyperplastic isthmic epithelium. Once again, note the lack of a granular layer.



with radical radiotherapy. There was no recurrence noted in the patients treated with MMS with a mean follow up of 14.4 months. Two recurrences occurred following WLE. All authors who recommended WLE advocated for at least 1 cm margins. Most authors recommend MMS if available as it provides complete histologic evaluation of the tumor margins and reduces the size of the surgical defect and resultant repair.[1,7,9,11,12]

DISCUSSION

PTT is a rare tumor as indicated by the dearth of reports in the literature over the last 13 years (Table 1). Due to its rarity and the resultant poor quality of data, as only case reports and case series are available, it is difficult to provide evidence-based guidelines. However, due to the potential for locally aggressive behavior, metastasis and malignant transformation with PTTs, we recommend MMS if tissue sparing is crucial to reduce patient morbidity and WLE with 1 cm margins is not feasible.

CONCLUSION

PTT is a rare but potentially aggressive tumor that should be treated by MMS, when possible, to reduce the rare but reported risk of local spread, metastasis, malignant transformation and recurrence.

TABLE 1.

Summary Data Reporting Proliferating Trichilemmal Tumor Between 2007 and 2020

Author/Year	Other	Cases Reported	Treatment	Outcome	Recommendation
Cecchi et al. 2008[6]	Case Report	1	MMS & sentinel lymph node biopsy	No recurrence or metastasis at 32 months	MMS is a suitable treatment option for recurrent malignant PTT
Sengul et al. 2010[7]	Case Report	1	WLE	No recurrence or metastasis at 40 months	WLE with long-term surveillance may be the best choice for both diagnosis and treatment
Deshmukh et al. 2014[8]	Case Report and Literature Review	1	WLE	WLE performed, no follow up reported	WLE, long term follow-up
Fieleke et al. 2015 [9]	Case Report	1	Conservative excision then MMS	No recurrence at 6 months after MMS	WLE with 1 cm margin; MMS provides superior margin control
Sutherland et al. 2017[10]	Case Report and Literature Review	1	Radical radiotherapy	Complete clinical response, no need for surgery at 29 months	Radical radiotherapy is a suitable alternative to surgery
Singh et al. 2018[11]	Case Report	1	MMS	WLE then recurrence within 6 months; MMS performed with no recurrence at 12 months	WLE with at least 1 cm margin. MMS may provide superior cosmetic result and similar recurrence rates.
Alarcón Pérez et al. 2019[12]	Case Report	3	Case 1: WLE Case 2 & 3: MMS	Case 1: No recurrence at 12 months Case 2: No recurrence at 17 months Case 3: No recurrence at 10 months	Surgical excision with at least 1 cm margin, MMS can also be considered.
Our Patients 2019–2020	Case Report and Literature Review	2	MMS for both cases	Case 1: No recurrence at 13 months Case 2: No recurrence at 11 months	MMS to ensure complete tumor clearance and optimize cosmesis, otherwise WLE with 1 cm margin.

MMS; Mohs micrographic surgery, WLE; Wide local excision

DISCLOSURES

None of the authors have any disclosures or conflicts of interest relating to this manuscript.

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CASE REPORT

Journal of Drugs in Dermatology

Severe Ulcerative Perniosis Treated With Abobotulium Toxin

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ABSTRACT

Perniosis (also known as pernio or chilblains), is a condition characterized by the development of pruritic, painful erythrocyanotic skin lesions induced by exposure to cold temperatures.[2] When perniosis occurs in conjunction with clinical or laboratory features of systemic lupus erythematosus, the condition is further classified as chilblain lupus erythematosus (CHLE). CHLE is a rare condition with limited treatment options especially in refractory cases.[3] Here we discuss the utility of therapeutic botulinum toxin injections in the treatment of severe, ulcerative CHLE.

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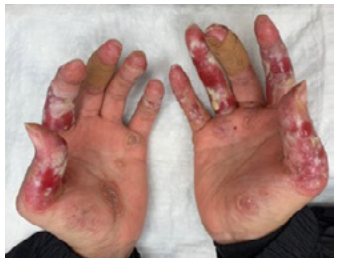
CASE

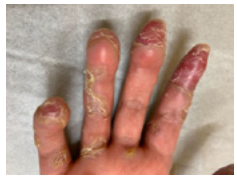
A 25-year-old female with a 9-year history of systemic lupus erythematosus (SLE) categorized by +ANA (1:640 speckled), +ds-DNA, +anti-Smith, +Anti-histone, palatal ulcers, hypocomplementemia (C3 and C4), malar rash, class V glomerulonephritis, discoid rash, non-scarring alopecia, arthralgias, myalgias and morning stiffness, was referred for management of severe desquamation of all finger tips, hyperextension of the thumbs, and violaceous hyperkeratotic plaques on the hands associated with shallow ulcerations and erosions (Figure 1). Medications for her SLE included aspirin (81 mg PO qd), belimumab (IV, q30d), hydroxychloroquine (400 mg PO qd), lisinopril (40 mg PO qd) and mycophenolate mofetil (500 mg PO bid).

FIGURE 1. Erythematous plaques with ulceration (December 7, 2020).



Her distal extremity symptoms first presented as painless livedo reticularis and progressed to include painful and pruritic lesions. Chilblain lupus erythematosus (CHLE) was suspected because of the patients underlying SLE diagnosis and chronicity and the absence of triphasic skin color changes typically seen in Raynaud's phenomenon (RP).[4] Moreover, although the lesions initially worsened in the winter months and healed during the summer months, they chronically worsened until they were persistent year-round (Figure 2). On presentation, her symptoms had developed into painful ulcers that prevented her from completing activities of daily living or working. She had to keep her hands wrapped in bandages at all times.

FIGURE 2. Fingertip desquamation and hyperkeratotic plaques (August 12, 2020).



Over a 5-year period, treatment with petrolatum ointment, neomycin and polymyxin ointment, mupirocin cream, 2.5% hydrocortisone cream, topical dapsone, pimecrolimus cream, betamethasone diproprionate ointment, clobetasol cream, pentoxifylline (400 mg tid), nifedipine (60 mg qd), prednisone (up to 40 mg qd), nitroglycerine paste, sildenafil (50 mg qd), and lifestyle modifications all failed. Workup and clinical evaluation were negative for evidence of systemic sclerosis (negative anti-Scl-70, anti-centromere antibodies, and no sclerodactyly) and antiphospholipid syndrome (APLS antibodies negative). Plain radiographs revealed soft tissue atrophy at the tip of the fingers and subluxation of right thumb interphalangeal joint. Upper extremity duplex studies did not reveal evidence of microvascular disease. Transthoracic echocardiogram failed to reveal valvular abnormalities.

DISCUSSION

CHLE is a very rare form of chronic cutaneous lupus erythematosus that presents with pernio persisting beyond the winter months.[2,3] Although the pathogenesis is not completely understood, it is thought to be associated with vasoconstriction and microvascular injury provoked by exposure to cold and damp environments.[3] On exam, patients classically present with pruritic, erythematous to violaceous macules, papules or plaques that can develop into blisters and ulcerations.[3]

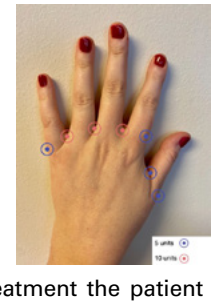
Treatment options for CHLE are limited and mostly confined to

traditional SLE therapeutics.[2,3] Nevertheless, these treatment options, which include topical and systemic steroids as well as systemic calcium inhibitors, only work to relieve symptoms in 50% of patients.[3] Some studies suggest the use of mycophenolate mofetil, antimalarial agents and topical tacrolimus or pimecrolimus but evidence is limited.[3] Moreover, as our patient had tried all of these therapies without symptom improvement, we attempted to treat with local injection of onabotulinumtoxinA (Botox).

To our knowledge, BTX injections have not been previously reported for the treatment of CHLE. However, local injection of BTX is a recently described alternative therapy for treatment resistant, severe ulcerative RP, which has a similar pathogenesis to CHLE.[2-5] Both RP and CHLE are associated with abnormal vasoconstriction in response to cold that manifests with chronic ischemia presenting with pain and in severe cases, ulceration.[2-5] Although the mechanism of action of BTX is not completely understood, it is known that BTX blocks the neurotransmitter response across the neuromuscular plate by inhibiting the release of acetylcholine.[5] As a result, BTX inhibits smooth muscle contraction and improves digital blood flow. BTX also affects the binding of soluble N-ethylmaleimide sensitive factor attachment protein receptors, inhibiting the release not only of acetylcholine, but also of a variety of other neurotransmitters like norepinephrine, substance P, calcitonin gene-related peptide and glutamate.[6] These neurotransmitters are components of several neuropathic pain pathways and thus, by inhibiting these neurotransmitters, BTX reduces pain severity.

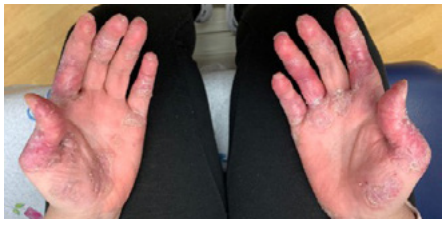
Fifty units of BTX were injected into each of the patients hands at 7 different locations (Figure 2).[1,4-6] 10 units were placed into each inter digital web space adjacent to the 2nd, 3rd and 4th common digital arteries (30 units per hand), and 5 units were placed at the proximal phalanx base of the radial aspect of the index finger, the ulnar side of the small finger, and at each side of the thumb (20 units per hand).[1] To treat both hands, a total of 100 units of BTX were used (see Figure 3 for injection protocol).

FIGURE 3. BTX injection protocol.



One month after treatment the patient reported improvement in pain and redness as well as increased finger mobility. On examination fingertip desquamation, erosion, skin induration and thickening of the distal fingertips, as well as hyperkeratotic plaques with some granulation tissue continued to be observed. However, the patient reported no longer needing to wear bandages throughout the day and was able to do more of her normal activities around the house. She also continued with clobetasol cream for the scaly areas and sildenafil and pentoxifylline along with her chronic SLE medications. Three months after treatment, digital ulcerations resolved completely, leaving only moderate desquamation of the digits and healing pink hyperkeratotic plaques (Figure 4).

FIGURE 4. Results after BTX injections (March 15, 2021).



This case suggests that local injection of BTX is an effective treatment option for CHLE in cases where traditional SLE therapeutics are ineffective. BTX seems to inhibit vascular spasms which reduces the severity of lesions and promotes healing of ischemic digital ulcerations. BTX injections offer a simple and non-invasive way to treat severe manifestations of CHLE and achieve safe and rapid results. In patients with CHLE that is resistant to traditional treatment, botulinum toxin injections should be considered.

DISCLOSURES

The authors declare that there is no conflict of interest.

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Decemer 2021 1353 Volume 20 • Issue 12

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Disseminate and Recurrent Infundibulofolliculitis: An Under-Recognized Yet Treatable Entity

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ABSTRACT

Disseminate and recurrent infundibulofolliculitis (DRIF) is a pruritic papular eruption that predominantly affects young adults with Fitzpatrick skin types 4-6. Due to DRIF's rarity and under-recognition, no standardized treatment guidelines exist. However, several oral agents have been used, including vitamin A, antibiotics, and retinoids. Topical agents, such as calcineurin inhibitors and mid-potency steroids, can also be efficacious. This brief communication summarizes treatments for DRIF in the published literature.

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INTRODUCTION

Disseminate and recurrent infundibulofolliculitis (DRIF) is a rare skin condition of unknown etiology first reported by Hitch and Lund in 1968.[1] In our clinical practice, we have encountered this condition infrequently, but it poses a significant therapeutic challenge. Characterized by skin-colored follicular papules on the trunk and proximal extremities, DRIF is more prevalent among young men of African descent and those with Fitzpatrick skin types 4-6.[1] The papules are pruritic and can demonstrate trichosis and become pustular.[1,5] DRIF is often self-limiting; however, the pruritic component can be bothersome.

The etiology of the condition is not known, and it is often misdiagnosed or underrecognized as a clinical entity. However, the pathophysiology is similar to other folliculitis disorders with an inflammatory infiltrate affecting the infundibulum.[1,2] As a consensus is lacking on standardized treatment of DRIF, clinician preference often drives treatment. The aim of this brief communication is to summarize effective treatments for DRIF.

METHODS

A search was conducted using the PubMed database. The following keywords were searched in batch phrases: disseminate, recurrent, infundibulofolliculitis, and treatment.

RESULTS

A variety of treatments have been used and have demonstrated success at alleviating DRIF symptoms (Table 1).[1-10]

DISCUSSION

Treatment of DRIF remains widely anecdotal. Oral vitamin A and isotretinoin can be efficacious due to their promotion of decreased follicular turnover and slower keratinization.[2,6,8] A combination of oral vitamins A and E appears to have beneficial outcomes as well. However, oral retinoids are often limited by their systemic side effects and resultant laboratory abnormalities. Although topical retinoids have not been trialed in literature, we contend that they would likely also be beneficial given similar mechanisms of action.

Alternative treatments with smaller sample sizes include light therapy, topical steroids, and topical calcineurin inhibitors. Narrow-band ultraviolet B therapy and methoxypsoralen plus ultraviolet A therapy(PUVA) promote altered cytokine expression, which can result in apoptosis and increased immunosuppression of Langerhans cells. Both topical steroids and calcineurin-based inhibition promote decreased inflammation and irritation. Antibiotics with added anti-inflammatory properties can reduce DRIF-associated infundibular swelling.[1,9,10]

With only a handful of DRIF cases documented, knowledge regarding disease maintenance and time course for treatment is limited. However, improvement typically occurs within 4 to 8 weeks. Relapse can occur, and it is unclear based on existing literature if repeat treatment with the same modality or adjunct therapy is necessary.

Ultimately, DRIF remains an uncommon and underdiagnosed

TABLE 1.

Summary of DRIF Treatment Methods from Past Research Studies

References	Study Type	Number of Subjects	Treatment	Outcome
Shakoei et al.[1]	Case Report	1	Oral doxycycline 100 mg QD	Significant improvement in pruritus and pustular lesions after 3 months
Owen and Wood[2]	Case Series	5	Oral vitamin A 50,000 units BID	Significant subjective and objective improvement after 4 to 8 weeks
Ravikumar et al.[3]	Case Report	1	PUVA: oral 8-methoxypsoralen then ultraviolet A exposure 2 hours later (start at 2 J and increase slowly to 8 J). Initial treatment three times a week. After 3 weeks, treatment twice a week for maintenance	Significant improvement in lesions after 3 weeks
Hinds and Heald[4]	Case Report	1	Fluocinonide cream (0.05%) QD. After 2 months, fluocinonide cream once a week for maintenance	Significant improvement in lichenification, pruritus, papules, and pustules after 2 months
Nair et al.[5]	Case Report	1	Narrow-band ultraviolet B and topical tacrolimus (0.1%)	Moderate improvement after 8 weeks
Çalka et al.[6]	Case Report	1	Oral isotretinoin 0.5 mg/kg QD	Significant improvement in lesions after 3 months
Aroni et al.[7]	Case Report	1	Oral isotretinoin 10 mg QD for 15 days, then 30 mg QD for 2 months	Remission after 45 days
Aroni et al.[8]	Case Report	1	Oral isotretinoin 0.6 mg/kg QD for 4 months	Remission after 4 weeks
Thew and Wood[9]	Case Report	1	Diphenhydramine hydrochloride 50 mg TID and triamcinolone cream (0.025%) locally	Significant improvement after 3 weeks. Two subsequent flares over following year; both spontaneously self-resolved
Hitch and Lund[10]	Case Report	2	Patient 1: Methdilazine hydrochloride 8 mg BID Patient 2: Trimeprazine and methdilazine hydrochloride (unspecified dose)	Patient 1: Asymptomatic after 2 weeks. Complete resolution after 5 months Patient 2: Questionable benefit but asymptomatic after 5 months

Legend: QD = Everyday, BID = Twice Daily, TID = Thrice Daily

disorder. A question that should arise in clinicians' minds when they encounter a patient with DRIF is whether the condition requires treatment. Factors such as the severity of the patient's DRIF and its impact on the patient's quality of life should be considered due to the often benign and self-limiting course of the condition.[2] Systemic therapies should be reserved for prolonged or recalcitrant disease.

This brief communication summarizes effective treatments for disseminate and recurrent infundibulofolliculitis and highlights a barrier to standardizing DRIF treatment. DRIF is often under-recognized, and identification is paramount for efficacious treatment. Clinicians should be aware that this skin condition can spontaneously resolve and the variety of modalities available for treatment.

DISCLOSURES

The authors declare no conflicts of interest or funding.

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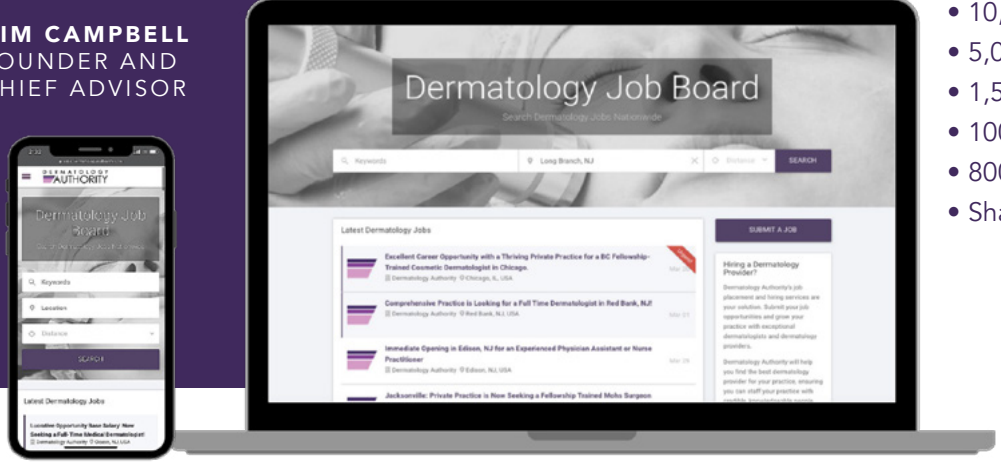

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Body Hair and Identity in Transgender Men: A Cross-Sectional Survey

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INTRODUCTION

Transgender and gender diverse people can experience increased depression, anxiety, suicidal ideation, and suicide from gender dysphoria (GD).[1] GD occurs due to a discrepancy between a person's gender identity, assigned gender, and physical characteristics.[2] Gender affirming medical care, including dermatologic care, can increase body-gender congruence and decrease negative outcomes associated with GD.[3,4,5]

Transgender and transmasculine men report chest hair is an important component of their gender identity and expression.[6] Transmen typically experience an increase in chest hair after starting testosterone therapy but have less chest hair than cisgender men.[7] However, studies in transmen examining identity and body hair elsewhere are limited. We developed a survey to evaluate the role of body hair in gender identity and sexual expression among transmen.

This study was deemed exempt by the Massachusetts General Brigham IRB. An anonymous online survey was posted in transmale-focused Facebook and Reddit pages. The survey was open to those over age 18 who identified as a gender minority and lived in the United States between December 2020 and February 2021. Only complete surveys by those who identified as transgender men or transmasculine were included in the results. Body hair was rated on a modified Ferriman-Gallwey Hirsutism Scoring System (FGS).[8] Gendered characteristics of the FGS were eliminated and a section on perineal and perianal hair was created.

A total of 444 of 508 surveys (87.4%) submitted by transmen or transmasculine-identifying participants were complete and included in analysis (Table 1). Participants were mostly Caucasian (77.3%) with an average age of 28.3 ± 9.1. Almost all participants reported current testosterone therapy (90.0%). Most transmen (88.3%) felt that body hair was an important factor contributing to positive self-image. Almost two-thirds (65.8%) of transmen reported that body hair was part of their sexual expression.

A majority felt that hair on the legs (78.8%), chest (68.7%), and arms (65.1%) was an important component of gender identity and expression. In contrast, most did not consider genital, perianal, or back hair to be as significant (Table 1). Compared to their current hair density, participants, on average, desired significantly greater hair density on their chest (Δ+66.7%, P=0.00), arms (Δ+28.0%, P=0.00), and legs (Δ+13.9%, P=0.00) and decreased perianal hair density (Δ-24.2%, P=0.00) as rated on the FGS (Table 2).

A minority (2.5%) reported use of treatments to increase body hair density. The most reported treatment was topical minoxidil (1.8%). Most participants (62.2%) reported that they would feel comfortable discussing body hair enhancement with a physician. However, only 22.7% had done so. The most common method by which participants heard of body hair enhancement was social media (4.9%). Only one participant reported seeking care from a dermatologist for body hair enhancement.

Transmasculine and transgender men report that body hair is important to their gender identity and sexual expression. Most desire substantially increased hair on the chest and extremities despite current testosterone use. However, few are treating with therapies beyond testosterone and almost none have consulted a dermatologist for body hair enhancement.

This study has several limitations including reliance on a self-reported online convenience sample. However, it is among the first reports of body hair density, gender identity, sexual expression, and treatment in transmen. Transmen are generally open to discussing body hair with their physician. We recommend dermatologists introduce this topic during visits relevant to gender transition, as it can legitimize patient concerns and open dialogue. While body hair enhancement in transmen remains a nascent area of study, it represents an opportunity for dermatologists to contribute to improved care for transgender and gender diverse people.

TABLE 1.

Demographics and Characterization of Desired Body Hair	
Surveys	
Surveys submitted	508
Transman or transmasculine identifying [included]	444
Not transman or transmasculine identifying [excluded]	64
Item, mean (SD)	
Age	28.3 ± 9.1
Race, Ethnicity, or Origin, n (%)	
American Indian or Alaska Native	5 (1.1)
Asian	8 (1.8)
Black or African American	27 (6.1)
Hispanic, Latino, or Spanish Origin	35 (7.9)
Middle Eastern or North African	3 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)
White	343 (77.3)
Other race, ethnicity, or origin	20 (4.5)
Chose not to disclose	2 (0.5)
Gender Identity, n (%)	
Man/Transman or transmasculine	444 (100)
Greater than 1 gender identity[a]	48 (10.8)
Body Hair and Identity, n (%)	
Body hair is important component of positive self-image	392 (88.3)
Body hair is part of sexual being and sexual expression	292 (65.8)
Body Hair Location and Gender Identity, n (%)	
Leg hair as an important component of gender identity	350 (78.8)
Chest hair as an important component of gender identity	305 (68.7)
Arm hair as an important component of gender identity	289 (65.1)
Genital hair as an important component of gender identity	193 (43.5)
Perianal hair as an important component of gender identity	73 (16.4)
Back hair as an important component of gender identity	69 (15.5)
Prior and Current Body Hair Treatments, n (%)	
History of current or prior treatment to increase body hair	11 (2.5)
Topical minoxidil	8 (1.8)
Vitamins or other supplements	8 (1.8)
Topical testosterone	3 (0.7)
Microneedling	2 (0.5)
Hair transplant	0 (0.0)
Photobiomodulation	0 (0.0)
Provider Comfort, n (%)	
Had brought up body hair with a provider in the past	101 (22.7)
Would feel comfortable discussing body hair with MD	276 (62.2)

[a]In addition to transman or transmasculine

TABLE 2.

Current and Desired Body Hair Scores Using a Modified[a] Ferriman-Gallwey Scale (FGS)[5]				
Body Hair Location	Current FGS	Desired FGS	Mean Difference (%)	*P* Value
Chest	2.4 ± 1.4	4.0 ± 1.1	+1.6 (+66.7)	0.00
Arms	2.5 ± 1.0	3.2 ± 1.1	+0.7 (+28.0)	0.00
Legs	3.6 ± 1.2	4.2 ± 1.0	+0.5 (+13.9)	0.00
Genital	3.2 ± 1.1	3.4 ± 1.0	+0.2 (+6.3)	0.00
Back	1.8 ± 1.1	2.0 ± 1.0	+0.2 (+11.1)	0.00
Perianal	3.3 ± 1.0	2.5 ± 1.2	-0.8 (-24.2)	0.00
Combined		**2.8 ± 1.1**	**3.2 ± 1.0**	**+0.4 (14.2)**

[a]Modification of FGS was limited to revision of gendered features on the scale. The minimum score of 1 represents no hair and the maximum score of 5 represents the greatest hair density.

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LETTER TO THE EDITOR

Journal of Drugs in Dermatology

Control of Diabetic Gustatory Hyperhidrosis With Topical 20% Aluminum Chloride Hexahydrate

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INTRODUCTION

Diabetic gustatory hyperhidrosis is a late sequela of diabetes and can have profound consequences. We report a case of diabetic gustatory hyperhidrosis controlled with topical aluminum chloride hexahydrate and support this as a first-line treatment. Aluminum chloride hexahydrate is a safe, effective, inexpensive and commercially available treatment.

CASE REPORT

A 62-year-old woman with a 25-year history of type-2 diabetes mellitus complicated by peripheral neuropathy presented with 20-lb weight loss over six months with coincident development of sweating and flushing of the bilateral preauricular and temporal skin. She had developed inexorable anxiety and embarrassment about the sweating and had begun to avoid eating. Comprehensive workup for other etiologies of her weight loss was negative and she was diagnosed with diabetic gustatory hyperhidrosis.

The patient was treated with topical 20% aluminum chloride hexahydrate in anhydrous ethanol applied at night to the areas of sweating using a roll-on applicator. After two weeks of nightly application, she reported dramatic improvement of the sweating, with no local or systemic side-effects. She was able to maintain control of her gustatory hyperhidrosis with application every third night. Over the next two months she gained 13 lbs. She reported normalization of food intake along with improved mood and resolution of anxiety associated with eating.

DISCUSSION

Prandial head and neck sweating and flushing in patients with long-standing diabetes suggests diabetic gustatory hyperhidrosis. Prevalence among type-2 diabetics is estimated to be 13%.[1] It was once believed to be caused by aberrant autonomic innervation, similar to the postulated mechanism of Frey syndrome. However, the observation that gustatory hyperhidrosis either disappears completely or improves significantly in diabetics after renal transplantation, has led to the suspicion of a metabolic etiology.[2]

There is a paucity of treatment options described in the literature which relieve sweating in diabetics with gustatory hyperhidrosis (Table 1). Topical glycopyrrolate preparations have been reported to be successful outside of the United States.[3] Isolated cases have reported use of oxybutynin with success, however, the associated systemic anticholinergic side effects make it less than ideal.[4,5] Injections of botulinum toxin-A are effective, but may be painful, have insurance coverage barriers, or be cost-prohibitive.[6] Topical aluminum chloride has been used successfully in treating gustatory hyperhidrosis in Frey syndrome, and but there is a scarcity of literature describing the successful use of aluminum chloride to treat diabetic gustatory hyperhidrosis.[7,8]

Aluminum chloride is an inexpensive medication used to reduce focal sweating. Aluminum ions form a precipitate with mucopolysaccharides in the sweat ducts, physically obstructing the flow of sweat and damaging epithelial cells along the lumen of the duct.[9] This obstruction is temporary however, and normal sweat gland function returns with epidermal renewal, thus necessitating continued therapy. In our patient, application

TABLE 1.

Common Treatments for Gustatory Hyperhidrosis

Medications	Efficacy	Low Cost/ Easy Insurance Approval	Common Side Effects
Topical 20% aluminum chloride hexahydrate	✓	✓	irritation, erythema, itching, redness
Topical anticholinergics (e.g. glycopyrrolate formulations)	✓	--	self-contamination to areas such as eyes and mouth
Botulinum toxin injections	✓	--	pain, focal muscle weakness
Oral anticholinergics (e.g. oxybutynin)	✓	✓	dry mouth, dry eyes, urinary retention, constipation

every third night adequately maintained control of symptoms. Most common side effects include irritation, stinging, burning, and dermatitis, especially on sensitive skin such as the face. It is important to counsel patients that aluminum chloride forms hydrochloric acid in the presence of water or active sweating.[10] Pre-washing the face or application before prandial sweating can lead to highly irritated skin and treatment discontinuation. We recommend patients apply aluminum chloride at night to thoroughly dried skin, and to completely wash it off in the morning.

Proper application enhances efficacy and reduces the incidence of adverse effects commonly seen with aluminum chloride. Our case supports the use of aluminum chloride hexahydrate for diabetic gustatory hyperhidrosis based on its efficacy, availability, favorable side-effect profile and low cost.

DISCLOSURES

Dr. Glaser received research/grants from Allergan, Galderma, Revance, Evolus, Dermira, Atacama and served on the advisory position or speaker from Allergan, Galderma, Dermira, Candasent, and is President of International Hyperhidrosis Society. Jordan Tanner and Dr. Daniel Tinker report no conflicts of interest.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

ARAZLO™ (tazarotene) Lotion, 0.045%

For topical use
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

CONTRAINDICATIONS

ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient *[see Warnings and Precautions, Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Embryofetal Toxicity Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, discontinue ARAZLO as soon as pregnancy is recognized.

Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for ARAZLO have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications, Use in Specific Populations]*.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. Tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

Advise pregnant patients of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to ARAZLO therapy. Initiate ARAZLO therapy during a menstrual period. Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO *[see Dosage and Administration in full Prescribing Information, Use in Specific Populations]*.

Skin Irritation Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. 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. Patients with sunburn should be advised not to use ARAZLO until fully recovered.

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

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections:

- Embryofetal toxicity *[see Warnings and Precautions]*
- Photosensitivity and Risk of Sunburn *[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 clinical practice.

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino and 42% were younger than 18 years of age, fourteen of 779 subjects (1.8%) treated with ARAZLO were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in Table 1. Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated. Overall, 2.4% (19/779) of subjects discontinued ARAZLO because of local skin reactions.

Table 1: Adverse Reactions Reported by ≥1% of the ARAZLO Group and More Frequently than the Vehicle Group

Adverse Reactions N (%)		
	ARAZLO Lotion N=779	**Vehicle N=791**
Application site pain[1]	41 (5)	2 (<1)
Application site dryness	30 (4)	1 (<1)
Application site exfoliation	16 (2)	0 (0)
Application site erythema	15 (2)	0 (0)
Application site pruritus	10 (1)	0 (0)

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

Skin irritation was evaluated by active assessment of erythema, scaling, itching, burning and stinging, with grades for none, mild, moderate, or severe. The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The percentage of subjects with these signs and symptoms at any post-baseline visit are summarized in Table 2.

Table 2: Incidence of Local Cutaneous Irritation at any Post-Baseline Visit

	ARAZLO Lotion N=774 Mild/Moderate/Severe	**Vehicle Lotion N=789** Mild/Moderate/Severe
Erythema	49%	38%
Scaling	51%	23%
Itching	29%	14%
Burning	30%	6%
Stinging	22%	5%

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with ARAZLO.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

In a trial of 27 healthy female subjects, between the ages of 20–55 years, receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, the concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and $AUC_{0\text{-}24}$ of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng•hr/mL, respectively) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., minipills) has not been evaluated.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary ARAZLO is contraindicated in pregnancy.

There are no available data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

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 equivalent to 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 15 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 1 and 30 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 6 times the MRHD (based on AUC comparison) *(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. 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.

Data *Animal Data* 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 (equivalent to 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 (15 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 1 and 30 times, respectively, the MRHD (based on AUC comparison).

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 (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this 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 the MRHD (based on AUC comparison).

Lactation

Risk Summary There are no data on the presence of tazarotene or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAZLO and any potential adverse effects on the breastfed child from ARAZLO.

Clinical Considerations To minimize potential exposure to the breastfed infant via breast milk, use ARAZLO for the shortest duration possible while breastfeeding. Advise breastfeeding patients not to apply ARAZLO directly to the nipple and areola to prevent direct infant exposure.

Females and Males of Reproductive Potential

Pregnancy Testing Pregnancy testing is recommended for patients of childbearing potential within 2 weeks prior to initiating ARAZLO therapy which should begin during a menstrual period.

Contraception Advise patients of childbearing potential to use effective contraception during treatment with ARAZLO.

Pediatric Use Safety and effectiveness of ARAZLO for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years and older based on evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled, 12-week clinical trials and an open-label pharmacokinetic study. A total of 300 pediatric subjects aged 9 to less than 17 years received ARAZLO in the clinical studies *[see Clinical Pharmacology and Clinical Studies in full Prescribing Information]*.

The safety and effectiveness of ARAZLO in pediatric patients below the age of 9 years have not been established.

Geriatric Use Clinical trials of ARAZLO did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

OVERDOSAGE

Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility 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 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 exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

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

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 equivalent to 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 tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 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 6 times the MRHD (based on AUC comparison).

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ARAZLO™
(tazarotene) Lotion, 0.045%
REDEFINE WHAT'S POSSIBLE

FOR YOUR PATIENTS WITH ACNE VULGARIS

CRACK THE TAZAROTENE CODE

ARAZLO is the first and only tazarotene lotion, formulated with polymeric emulsion technology, to help deliver the clearance you expect and the tolerability you want[1-3]

- Treatment success* rates were 26% for ARAZLO Lotion vs 13% for vehicle in study 1 and 30% vs 17%, respectively, in study 2 ($P<0.001$ in both studies)[1,4†]
- Most common adverse events (≥1% of patients and greater than vehicle) at application site were pain (5%), dryness (4%), exfoliation (2%), erythema (2%), and pruritus (1%)[1†]

SEE WHAT'S POSSIBLE AT ARAZLO.COM

*Treatment success on the Evaluator's Global Severity Score (EGSS) was defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1).[1]

†**Phase 3 study design:** The safety and efficacy of ARAZLO Lotion were assessed in 2 multicenter, randomized, double-blind clinical trials of 1,614 subjects aged 9 years and older with facial acne vulgaris. Subjects had a score of moderate (3) or severe (4) on the EGSS, 20 to 50 inflammatory lesions, 25 to 100 noninflammatory lesions, and 2 or fewer facial nodules.[1]

Indication

ARAZLO™ (tazarotene) Lotion, 0.045% is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

Important Safety Information

ARAZLO Lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.

Contraindication

ARAZLO Lotion is contraindicated in pregnancy due to the potential harm to the fetus.

Warnings and Precautions

Embryofetal Risk Females of childbearing potential should be warned of the potential risk and should use adequate birth-control measures when ARAZLO Lotion is used. A negative result for pregnancy should be obtained within 2 weeks prior to ARAZLO Lotion therapy, and therapy begun during a menstrual period. If the patient becomes pregnant while using ARAZLO Lotion, treatment should be discontinued.

Skin Irritation Patients using ARAZLO Lotion may experience application site pain, dryness, exfoliation, erythema, and pruritus. Depending upon severity, adjust or interrupt dosing as needed, increasing or resuming treatment as tolerated. Avoid application of ARAZLO Lotion to eczematous or sunburned skin.

Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

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

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (in ≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. ARAZLO Lotion [prescribing information]. Bridgewater, NJ. Bausch Health US, LLC. **2.** Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol*. 2019;18(6):542-548. **3.** Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed October 20, 2020. **4.** Data on file.

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