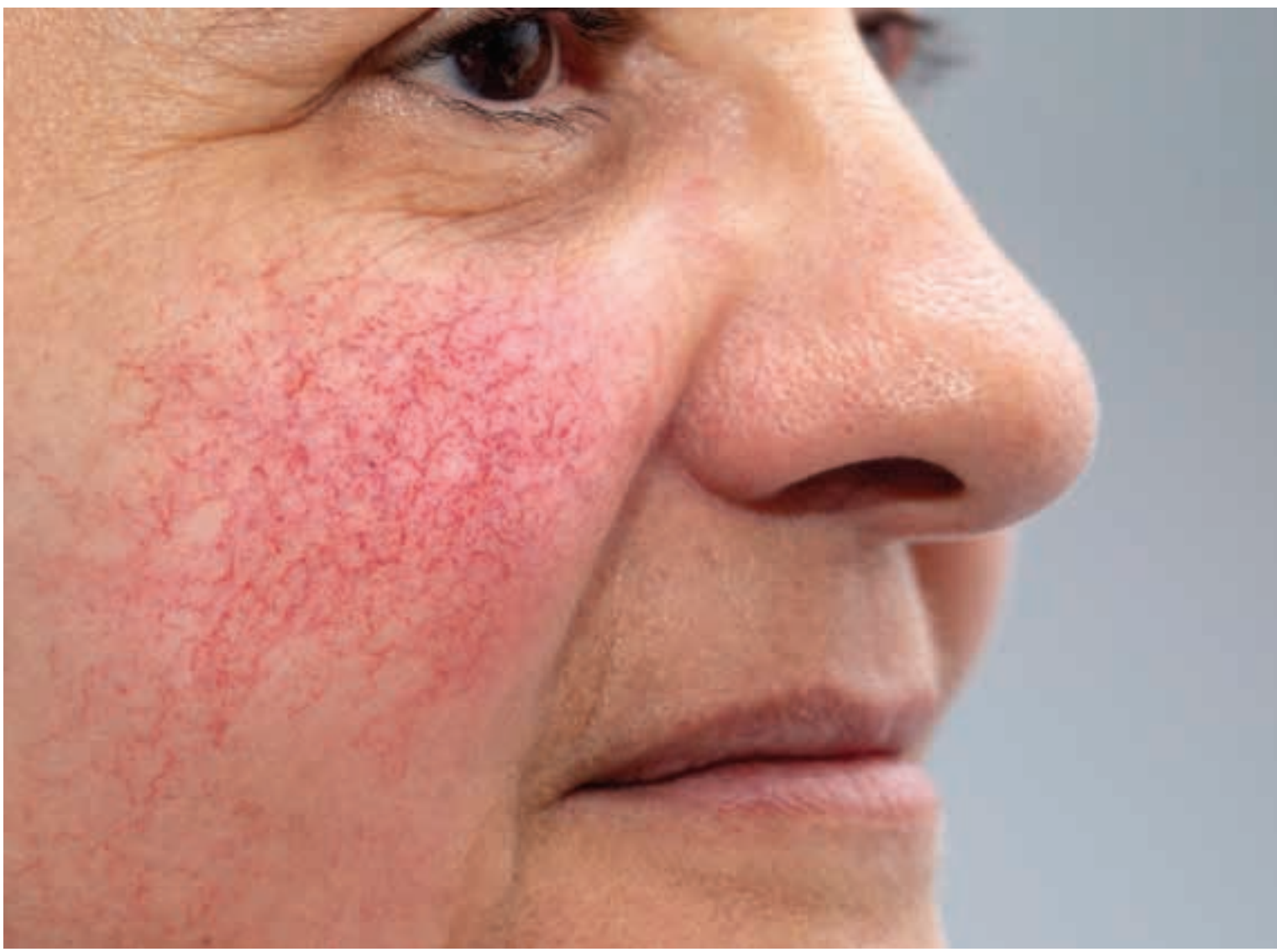
A SUPPLEMENT TO Dermatology News

JULY 2020

ACNE & ROSACEA



IN THIS ISSUE

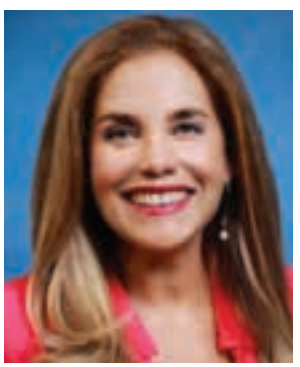
WITH COMMENTARY BY DR. HILARY E. BALDWIN

Maximizing the care of our unique patients

By Hilary E. Baldwin, MD

Do you ever wonder why acne and rosacea, like peanut butter and jelly or salt and pepper, always travel together? They are joined at the hip in American Academy of Dermatology clinical symposia, books, and chapters – and as a direct result – internet blogs. This suggests a murkiness in our diagnostic abilities that is fallacious.

There are obvious similarities: facial location, the presence of papules and pustules, and clinical response to the tetracyclines. But clearly, they are distinct entities with different demographics, pathophysiology, clinical presentation, and response to therapy. We don't do the same with atopic dermatitis and psoriasis, even though they are both red and scaly and respond to steroids. Clustering acne and rosacea implies a level of similarity that doesn't exist, diminishes their distinct therapeutic needs, and blurs the unique disturbances in quality of life from which our patients suffer. The articles chosen for this compilation of newsworthy, clinically useful stories on acne and rosacea published in *Dermatology News* over the past year highlight their differences and help us to maximize the care of our unique patients who have a clear and unequivocal diagnosis.



Dr. Baldwin

Having gotten that off my chest, I ironically lump them together and say it's a great time to be interested in acne and rosacea. We have made enormous strides in both diseases over the last 10 years. Our understanding of the pathophysiology of both diseases has been clarified, myths have been debunked, new therapies introduced, and old but great drugs reevaluated.

Rosacea, in particular, has been reimagined. Gone are the "subtypes" that attempted to squeeze patients with multiple disease manifestations into artificial pigeon holes. We celebrate the introduction of new, highly efficacious rosacea drugs that have narrow targets specific to the patient's needs.

In acne, the recent release of many new products and the rich acne pipeline nicely augment our toolbox and improve our therapeutic prowess.

Lastly, we have a call to arms: Dermatologists must increase their presence on social media. Although I personally fail to understand the impulse, patients turn to social media for medical information. Unfortunately, the Internet is awash in misinformation regarding these two diseases. Sources of the half-truths include the innocent (bloggers with good intentions but insufficient knowledge) and the stained (self-promoters and those seeking personal gain). Since we can't stop them, it's time for us to join them, to provide excellent unbiased and honest medical information with which patients can put their best face forward.

> *Our understanding of the pathophysiology of both diseases has been clarified, myths have been debunked, new therapies introduced, and old but great drugs reevaluated.*

Dr. Baldwin is a board-certified dermatologist who is medical director of the Acne Treatment & Research Center in New York. She is also clinical associate professor in the department of dermatology, Rutgers Robert Wood Johnson Medical Center in New Brunswick, N.J. She was a founding board member and second president of the American Acne & Rosacea Society. Dr. Baldwin is on the speaker's bureau of and is an adviser to Galderma, Ortho Dermatologics, Foamix Pharmaceuticals, Almirall, and La Roche-Posay, as well as an adviser to Mayne Pharma, Cassiopea, Sol-Gel, and EPI Health.

Dermatology News

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ARAZLO™
(tazarotene) Lotion, 0.045%

REDEFINE WHAT'S POSSIBLE

NEW!

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†]

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*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 10, 2019. **4.** Data on file.

Ortho Dermatologics

ARAZLO™ (tazarotene) lotion, for topical use
Initial U.S. Approval: 1997
This Brief Summary does not include all the information needed to use ARAZLO safely and effectively; please see full Prescribing Information for ARAZLO.

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, 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_{0-24} 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]*.

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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Target rosacea treatment to pathogenic pathway

PAPULES AND PUSTULES, TELANGIECTASIAS, ERYTHEMA, PHYMA NEED A TAILORED APPROACH

By Elizabeth Mechcatie
REPORTING FROM SDEF HAWAII DERMATOLOGY SEMINAR

LAHAINA, HAWAII – The pathophysiology of rosacea is complicated, which is why "we try to target our treatments to various areas in this pathogenic pathway" to achieve optimal results, according to Linda Stein Gold, MD, director of dermatology research at the Henry Ford Health System in Detroit.

For example, in a patient with papules and pustules, a topical or oral anti-inflammatory agent is needed "to calm that down." If background erythema is present, separate from papules and pustules, use a topical alpha-adrenergic agonist, she advised. For telangiectasias, consider a device-based treatment, and for a phyma, a surgical approach, she recommended at the Hawaii Dermatology Seminar provided by Global Academy for Medical Education/Skin Disease Education Foundation.

For the background erythema of rosacea, the two alpha-adrenergic receptor agonists available, brimonidine gel 0.33%, approved by the Food and Drug Administration in 2013, and oxymetazoline cream 1%, approved in 2017, both work on the neurovascular junction, but on different receptors.

Brimonidine "kicks in very, very rapidly," with a significant decrease in background erythema evident within 30 minutes and improvements that last over a 12-hour day, she said. It is effective over a year, but in long-term and postmarketing studies, about 20% of patients experienced exacerbation of erythema, with two peaks of redness. "One occurs at 3-6 hours," and the other peak occurs when the drug is wearing off later in the day, Dr. Stein Gold said.


Dr. Stein Gold

A study that sought to identify factors that might make patients more prone to this adverse effect found that "less is better" regarding brimonidine application, with an optimal application of one to three pea-sized dollops on the face, not five as instructed in the package insert. In addition, patients with more than five flushing episodes a week, particularly women, "tend to have more labile disease and [are] more likely to get that rebound erythema," the study found.

Oxymetazoline 1% in a cream formulation has a "slightly more gentle onset of action and a more gentle offset of action," without exacerbation of erythema and has been shown to have sustained efficacy over 52 weeks. In a yearlong safety study, there were "no new red flags and we weren't seeing that redness at hours 3-6, or even when you take the patient off the drug," she noted.

Dr. Stein Gold reported that she has served as a consultant, investigator, or speaker for Galderma, Dermira, Foamix Pharmaceuticals, Valeant, Allergan, Actavis, and Roche.

SDEF/Global Academy for Medical Education and this news organization are owned by the same parent company.

emechcatie@mdedge.com

Commentary by Dr. Baldwin / In 2002, the National Rosacea Society expert committee published a standard classification of rosacea, recommending that patients be partitioned into the subtypes of erythematotelangiectatic, papulopustular, phymatous, and ocular. At the time, it was a crucial step toward standardizing the description of an individual rosacea patient. Prior to that, case reports and studies simply referred to the patients as having "rosacea" as if that defined all manifestations in all patients with the disorder. Resulting therapeutic recommendations were dubious.

This classification system was never intended to be a final diagnostic reference, but rather, a temporary solution to a major problem. Beginning in 2007, the shortcomings of this system were evaluated and since then, many groups – including the NRS Expert Committee, the American Acne and Rosacea Society, and the global Rosacea Consensus panel (ROSCO) – have recommended a phenotypic approach. They note that patients rarely fit squarely into the subtype pigeon holes but rather have a constellation of signs and symptoms that defy the subtype boundaries. Furthermore, each aspect of the individual's disease deserves and requires independent consideration.

The most important outcome of the phenotypic classification concept is the recognition that most patients have combination disease and that combination disease requires combination therapy. There are medications appropriate for papules and pustules that fail to improve centrofacial erythema, and the alpha-agonists, which reduce erythema, have no impact on inflammatory lesions. Telangiectasias require physical modalities such as intense pulsed light or vascular lasers. Phymatous disease may respond to isotretinoin but usually requires physical ablation.

The ultimate goal of the phenotypic classification is optimization of patient care. Ideally, while the patient is looking at his/her own reflection, the clinician performs a careful examination, pointing out each manifestation of rosacea. Treatment options for each finding are discussed individually. Although therapeutic recommendations are based on clinical findings, patient preferences should be factored in as well. Rosacea is a chronic disease that will require chronic therapy – often more than one chronic therapy – and it is important that the patient is comfortable with the overall plan of action. Often, a patient with combination disease is more bothered by one aspect than another. Many have a preference for oral or topical medication, and some patients are more side-effect averse than others. Branded products and physical modalities may not be covered by insurance and can be quite costly. By combining phenotype-directed recommendations with patient preference, an ideal treatment plan can be instituted that is truly individualized.

Newer acne options may benefit black patients

LESS IRRITATING TREATMENTS POSE LOWER RISK OF EXACERBATING PIH

By Ted Bosworth
EXPERT ANALYSIS FROM SOC 2019

NEW YORK – The most recently approved therapy for acne, sarecycline, as well as several agents in late stages of clinical testing, might represent a particular advance for treating black patients or others with darker skin tones because of a reduced risk of irritation, according to a review presented at the Skin of Color Update 2019.

Acne is an inflammatory skin disease, but patients with darker skin tones are at a high risk of postinflammatory hyperpigmentation (PIH), a complication many consider worse than the acne itself, according to Andrew Alexis, MD, director of the Skin of Color Center and chair of the department of dermatology at Mount Sinai St. Luke's, New York.


Dr. Alexis

"The importance of PIH is that it alters our endpoint in patients of color. Not only are we treating the pustules, comedones, and other classic features of acne, but we have to treat all the way through to the resolution of the PIH if we want a satisfied patient," he said.

There are data to back this up. In one of the surveys cited by Dr. Alexis, 42% of nonwhite patients identified resolution of PIH as the most important goal in the treatment of their acne.

As in those with light skin, acute acne lesions in darker skin can resolve relatively rapidly after initiating an effective regimen that includes established therapies such as retinoids or antibiotics. However, PIH, once it develops, might take 6-12 months to resolve, according to Dr. Alexis, who is a professor of dermatology at the Icahn School of Medicine at Mount Sinai, New York.

"You have to keep in mind the subclinical inflammation, which can be a slow burning process beneath the surface of the skin," he said. He cited a biopsy study that demonstrated inflammation even in nonlesional skin of black patients with acne.

Because of the slow reversal of PIH, it is imperative in skin of color patients to employ therapies with the least risk of exacerbating PIH. While this includes judicious use of currently available agents, Dr. Alexis believes that newer agents might have a larger therapeutic window, reducing the potential for inflammation at effective doses.

This advantage has yet to be confirmed in head-to-head studies, but Dr. Alexis is optimistic. In the case of sarecycline, which became the first antibiotic approved specifically for acne when it was approved by the Food and Drug Administration in 2018, about 20% of those included in the phase 3 registration trial were nonwhite, he said.


Hulldude30/Getty Images
Once it develops, PIH can take 6-12 months to resolve, according to Dr. Andrew Alexis.

The results were "impressive" regardless of skin color in the phase 3 study, according to Dr. Alexis. He conceded that this is not the only antibiotic with anti-inflammatory activity, but he suggested that a high degree of efficacy might be relevant for early acne control and a reduced risk of PIH.

The same can be said for trifarotene, a novel topical retinoid that was associated with highly significant reductions in both inflammatory and noninflammatory lesion counts in a recently published phase 3 trial (J Am Acad Dermatol. 2019 Jun;80[6]:1691-

CONTINUED ON FOLLOWING PAGE

Commentary by Dr. Baldwin / Vehicle technology has come a long way in improving the efficacy of topical acne products. Perhaps even more importantly, advances in formulation science have led to superior tolerability of products containing inherently irritating substances such as benzoyl peroxide and retinoids. There are patient populations in which the delicate balance of efficacy and tolerability are of particular importance. Nowhere is this more important than in patients with skin of color.

Patients with skin types IV-V in particular have a tendency to hyperpigment in response to relatively minor assaults, such as medication-induced irritation. This leads to a Catch-22: Aggressive therapy is warranted to improve acne ASAP, to reduce postinflammatory hyperpigmentation from the lesions themselves, but irritation from stronger topical drugs can cause additional hyperpigmentation. One answer is to avoid topical medications altogether and increase the use of oral antibiotics, hormonal therapy, and isotretinoin. However, long-term use of antibiotics is imprudent, hormonal therapy is an option for women only, and isotretinoin is not appropriate for all patients.

Fortunately, however, our current and future acne toolbox includes a whole host of well-tolerated topicals. Micronization, unique formulations, low concentrations, and inclusion of humectants, emollients, and occlusives have greatly improved tolerability. Tretinoin 0.05% lotion and the soon-to-be released tazarotene 0.045% lotion are formulated in a unique polymeric emulsion that spreads the active ingredient evenly and incorporates moisturizing ingredients. Trifarotene, in the cream formulation, binds exclusively to the gamma-receptor, the most prevalent retinoic acid receptor in the skin, allowing for a very low concentration of 0.005%. Minocycline 4% foam is inherently nonirritating, but additionally, is formulated in a unique lipophilic foam vehicle. All should hit the sweet spot of the efficacy-tolerability trade-off.

Topical clascoterone under review at FDA

NOVEL TREATMENT TARGETS ANDROGEN RECEPTORS

By Bruce Jancin

REPORTING FROM THE SDEF HAWAII DERMATOLOGY SEMINAR

LAHAINA, HAWAII – Clascoterone cream, a first-in-class topical selective androgen receptor inhibitor for the treatment of acne now under review by the Food and Drug Administration, is already generating considerable buzz in the patient-advocacy community even though the agency won't issue its decision until August.

"I've actually had a lot of interest in this already from parents, especially regarding girls who have very hormonal acne but the parents are really not interested in starting them on a systemic hormonal therapy at their age," Jessica Sprague, MD, said at the SDEF Hawaii Dermatology Seminar provided by the Global Academy for Medical Education/Skin Disease Education Foundation.

Dr. Sprague

Clascoterone targets androgen receptors in the skin in order to reduce cutaneous 5-alpha-dihydrotestosterone.

"It's being developed for use in both males and females, which is great because at this point there's no hormonal treatment for males," noted Dr. Sprague, a pediatric dermatologist at Rady Children's Hospital and the University of California, both in San Diego.

The manufacturer's application for marketing approval of clascoterone cream 1% under FDA review includes evidence from two identical phase 3, double-blind, vehicle-controlled, 12-week, randomized trials. The two studies included a total of 1,440 patients aged 9 years through adulthood with moderate to severe facial acne vulgaris who were randomized to twice-daily application of clascoterone or its vehicle.

The primary outcome was the reduction in inflammatory lesions at week 12: a 46.2% decline from baseline with clascoterone 1% cream, which was a significantly greater improvement than the 32.7% reduction for vehicle. The secondary outcome – change in noninflammatory lesion counts at week 12 – was also positive for the topical androgen receptor inhibitor, which achieved a 29.8% reduction, compared with 18.9% for vehicle. Clascoterone exhibited a favorable safety and tolerability profile, with numerically fewer treatment-emergent adverse events than in the vehicle control group. A stronger formulation of the topical agent is in advanced clinical trials for the treatment of androgenetic alopecia in both males and females.

Dr. Sprague reported having no financial conflicts regarding her presentation.

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Commentary by Dr. Baldwin / Treating mild acne is accomplished with relative ease, often with monotherapy. Once it has advanced to moderate severe, however, treatment is more complicated and generally requires polytherapy. It takes multiple therapies to target the multifactorial acne pathophysiology, and on average, the successfully treated acne patient is on 2.53 medications. A typical regimen may involve drugs with antibacterial effects (topical and oral antibiotics, benzoyl peroxide, and isotretinoin), drugs that inhibit follicular keratinization (topical retinoids and isotretinoin), drugs with anti-inflammatory properties (retinoids, antibiotics, dapsone, and isotretinoin), and drugs that inhibit sebaceous gland function (antiandrogens, estrogen, and isotretinoin). Only isotretinoin covers all four of the pathogenic mechanisms and is the only medication that functions well as monotherapy for more severe acne.

Currently, the only medications available in the United States that inhibit sebaceous gland function are administered orally: combination contraceptives, spironolactone, and isotretinoin. Additionally, isotretinoin is not appropriate for use in all patients, and oral contraceptives and spironolactone cannot be used in male patients. The introduction, therefore, of a topically administered antiandrogen has been much awaited. It means that all four pathogenic factors of acne can be addressed with a combination of topical-only products and that this can be done in both women and men. In the phase 3 clinical trials, clascoterone looks to be efficacious and well tolerated and should be an excellent addition to our acne toolbox.

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9). According to Dr. Alexis, the impact of this therapy on PIH has not been specifically tested, but he expects those data to be forthcoming.

A new 0.045% lotion formulation of tazarotene might also widen the therapeutic window relative to current tazarotene formulations based on clinical trials he cited. Despite a concentration that is about half that of the currently available tazarotene cream, the efficacy of this product appeared to be at least as good "without the baggage of a greater potential for irritation," he said.

After "a few years of drought" regarding new options for treatment of acne, these are not the only promising agents in clinical trials, according to Dr. Alexis. If these agents prove to offer greater efficacy with less irritation, their increased clinical value might prove most meaningful to patients with darker skin.

"There is a delicate balance between maximizing efficacy without causing irritation that leads to PIH in patients with skin of color," he cautioned. He is hopeful that the newer agents will make this balance easier to achieve.

Dr. Alexis has financial relationships with many pharmaceutical companies, including many that market drugs for acne.

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Consider adding chemical peels to acne regimen

BENEFITS SHOWN WHEN COMBINED WITH OTHER THERAPIES

By Kari Oakes

EXPERT ANALYSIS FROM WCD2019

MILAN – Chemical peels are effective for many medical indications, but a mild peel can really shine as a treatment for acne, according to Dee Anna Glaser, MD.

Speaking at the World Congress of Dermatology, Dr. Glaser, director of clinical research and interim chair of the department of dermatology at Saint Louis University, said that, in her practice, acne and actinic keratosis are the most common medical indications for chemical peels and that "acne is just a winner all the way around."

For acne, she added: "Chemical peels can help both the comedonal and the inflammatory component. It should probably be combined with other therapies, and it does produce both an exfoliative and an anti-inflammatory benefit."

A variety of chemical peel formulations can be considered for acne, Dr. Glaser noted. "Typically, you're going to use a light chemical peel," such as glycolic or salicylic acid. Other options include Jessner's solution or a light trichloroacetic acid formulation, she said, adding that tretinoin alone can also be considered.

In choosing between glycolic and salicylic acid, Dr. Glaser said, "salicylic acid should theoretically be the best agent because it is lipophilic and the glycolic acid is hydrophilic." The reality of how these agents perform clinically, though, may sort out differently.

Dr. Glaser pointed to a double-blind, randomized, controlled trial of the two agents in 20 women with facial acne. The severity of participants' inflammatory acne was mild to moderate, with an average of 27 inflammatory lesions, and they had been on a stable prescription or over-the-counter acne regimen for at least 2 months (Dermatol Surg. 2008 Jan;34[1]:45-50).

Patients received six peels – one every 2 weeks – with 30% glycolic acid (an alpha-hydroxy acid) and 30% salicylic acid (a beta-hydroxy acid) in the split-face study.

All participants started at 4 minutes of exposure and increased up to 5 minutes as tolerated, although timing is really important only for glycolic acid, the same duration of exposure was maintained for each agent for the sake of consistency between arms, said Dr. Glaser, one of the investigators.

Sharing photographs of study participants, she observed that, after six peels, "there really isn't a significant difference." Therefore, she added, "even though salicylic acid should be better, you can see that glycolic acid really held its own in this study."

Dr. Glaser pointed out that a trend was seen for slightly better results with salicylic acid and results with this agent were more durable than those seen with glycolic acid. Patients reported fewer side effects on the beta-hydroxy–treated side as well.

She referred to another study, conducted in Japan, that used a double-blind, split-face design to compare 40% glycolic acid with a placebo that had a similarly low pH of 2.0. The 26 patients with moderate acne received five peels on a biweekly schedule, with glycolic acid significantly outperforming placebo. Among acne subtypes, noninflammatory acne improved more than inflammatory acne with glycolic acid (Dermatol Surg. 2014 Mar;40[3]:314-22).

Dr. Glaser said that, in her own practice, she still tries to use salicylic acid for her acne patients," though some patients prefer the experience of a glycolic acid peel, with which there's likely to be less pain. "So if you have a preference, or your patient has a preference, you will probably be able to use the acid that works best for you," she said.

Whatever peel is chosen, it should be considered an adjuvant to other topical and systemic acne therapies, Dr. Glaser stressed. "To maintain the results, you really do need to maintain the patient on some sort of standard acne therapy that you would normally do."

Peels can also be an effective part of a multipronged approach that includes laser therapy and intralesional steroids, she said. However, peels can be considered for monotherapy in patients who don't tolerate other acne therapies, and they can be used safely in pregnancy, she said.

As with all such treatments, dermatologists should remember to consider and counsel about herpes simplex virus prophylaxis and sun protection.

Dr. Glaser reported financial relationships with Galderma, Ulthera, Ortho, Allergan, Cellgene, and other pharmaceutical companies.

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Commentary by Dr. Baldwin / Many papers have extolled the virtues of chemical peels for the treatment of acne. Although they may be useful as monotherapy in mild disease, their primary benefit is in acting as an adjunct to traditional acne therapy. Along with other physical modalities, such as microdermabrasion, comedone extraction, intralesional corticosteroids, and laser and light, chemical peels may offer several benefits.

Patient adherence to an acne regimen is notoriously poor. Teenagers in particular have difficulty sticking to treatment plans long enough for them to have an effect. Most acne medications take weeks to months to kick in and anything that can be done to speed lesion resolution and visibly demonstrate efficacy will encourage compliance. Physical modalities, particularly comedone extraction and intralesional injections, produce immediate improvement to the delight of the patient.

In addition to treating acne, adjunctive procedures can improve scars, postinflammatory hyperpigmentation, and postinflammatory erythema, which are often more bothersome than the lesions themselves. Many patients prefer physical treatments over acne products. These techniques are perceived as being more modern, safer, and more "natural," and are far less work than daily use of acne medications. Lastly, they offer an opportunity for treatment of the pregnant patient.

We need to remind the patient, however, that adjunctive treatments are just that – adjuncts – and they do not take the place of traditional therapy.

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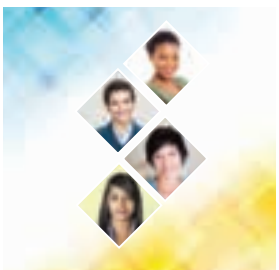

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Isotretinoin and psychiatric conditions

STUDY OF ADVERSE EVENT REPORTS DOES NOT SUPPORT A CAUSAL LINK

By Heidi Splete
FROM JAMA DERMATOLOGY

Isotretinoin use may increase vulnerability to psychiatric conditions, but available evidence does not support a causal relationship, on the basis of data from a retrospective study of 17,829 psychiatric adverse events reported to the Food and Drug Administration over 2 decades.

"Although one study highlighted consistent reporting of depression and suicide in patients taking isotretinoin in the United States from 1982 to 2000, few studies have examined reports of psychiatric adverse events at the national level since 2000," wrote Sean Singer of Harvard University, Boston, and his colleagues.

> *Few studies have examined reports of psychiatric adverse events at the national level since 2000.*

They reviewed data from the FDA's Adverse Event Reporting System between 1997 and 2017. A total of 17,829 psychiatric adverse events in which isotretinoin was the primary suspect drug were reported during the study period. The researchers classified the events into 12 categories; the most common were depressive disorders (42%), emotional lability (17%), and anxiety (14%). The number of reported psychiatric adverse events was similar between men and women (8,936 and 8,362 events, respectively).

The researchers also identified 2,278 reports of suicidal ideation, 602 reports of attempted suicide, and 368 reports of completed suicide.

In addition, the researchers examined data from the iPLEDGE program and found completed suicide rates of 8.4 per 100,000 patients in 2009 and 5.6 per 100,000 patients in 2010. However, these rates were lower than national suicide rates in the general population of 11.8 per 100,000 people in 2009 and 12.1 per 100,000 people in 2010.

Patient age was available for 13,553 adverse event reports, and patients aged 10-19 years accounted for 53% of the reports overall and 58% of completed suicides for which age was reported.

The high number of psychiatric adverse events in the youngest age group "could reflect more isotretinoin prescriptions in this age group or may suggest that teenagers are particularly vulnerable to psychiatric adverse events while taking isotretinoin," the researchers said.

The findings were limited by several factors, including the reliance on proper clinician reports to the Adverse Event Reporting System database and the separation of some psychiatric terms into categories that may reflect symptoms of other psychiatric diagnoses, the researchers said.

However, "Our data showed high numbers of reports of emotional lability, anxiety disorders, insomnia, self-injurious behavior, and psychotic disorders with isotretinoin as the primary suspect drug," they noted.

"Although no causal link has been established between isotretinoin and psychiatric adverse events, it is important to recognize that there are data that suggest patients using this drug may be vulnerable to a number of psychiatric conditions" and that monthly iPLEDGE visits are an opportunity to screen patients for these conditions, they said.

They also stressed that "the risk of psychiatric adverse events in patients taking isotretinoin must be considered in the context of a known increased risk of suicidal ideation in patients with acne independent of isotretinoin therapy."

Mr. Singer had no financial conflicts to disclose. Study coauthor John S. Barbieri, MD, disclosed partial salary support from Pfizer and grand support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Arash Mostaghimi, MD, disclosed personal fees from Pfizer.

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SOURCE: Singer S et al. JAMA Dermatol. 2019 Jul 3. doi: 10.1001/jamadermatol.2019.1416.

Commentary by Dr. Baldwin / Yet another paper suggests that depression, suicidal ideation, and suicide attempt/completed suicide is actually lower in patients on isotretinoin than in the general population of the United States. Once again, we are reminded to look not just at the numerator but also the denominator.

The rate of depression increases in the general population from childhood through adolescence and into young adulthood, right at the apex of isotretinoin use. Suicide is the leading cause of death in children aged 12-17 years and the third in those aged 15-19 years. The World Health Organization has found that half of all mental health conditions start by age 14.1 years (www.who.int/news-room/fact-sheets/detail/adolescent-mental-health).

In patients with acne, the stakes are raised. Halvorsen et al. noted, in a large cohort of acne sufferers, an overall prevalence of suicidal ideation of 10.9% (J Invest Dermatol. 2011 Feb;131[2]:363-70). Rates increased as acne severity worsened to a high of 24.1% among the most severe patients; by definition, patients taking isotretinoin have severe disease. The authors concluded that acne is an independent risk factor for suicidal ideation, especially among boys.

This is not to diminish the psychological dysfunction seen in acne patients on isotretinoin – it's just not clear that there is a causal link. Singer et al. noted many psychiatric adverse events in their large retrospective study. Our patients on isotretinoin are suffering – whether a factor of their age, their diagnosis of acne, or use of isotretinoin, and ultimately, it really doesn't matter why. It is our obligation to tend to the mind as well as the skin during our iPLEDGE-mandated monthly meetings.

Fetal exposure to isotretinoin continues

6,740 PREGNANCIES REPORTED TO FDA OVER 10-YEAR PERIOD

By Jeff Craven
FROM JAMA DERMATOLOGY

The number of pregnancies among women taking isotretinoin has decreased since the introduction of the iPledge program, but pregnancy, abortions, and fetal defects associated with isotretinoin exposure are still occurring in women of reproductive age, according to a retrospective study published in JAMA Dermatology.

In 2006, the Food and Drug Administration implemented the iPledge program, with requirements that include women of childbearing age having a negative pregnancy test and evidence of using two forms of contraception monthly to use isotretinoin, a teratogen. "Although the number of pregnancy-related adverse events for patients taking isotretinoin has decreased since 2006, pregnancies, abortions, and fetal defects associated with isotretinoin exposure continue to be a problem," Elizabeth Tkachenko, BS, from the University of Massachusetts Medical School, Worcester, and coauthors concluded. "Further research is required to determine the most efficacious system to reduce complications for patients and administrative requirements for physicians while at the same time maintaining access to this important drug." (iPledge followed other Risk Evaluation and Mitigation Strategy systems for isotretinoin.)

She and her colleagues performed a retrospective evaluation of pregnancy-related adverse events related to isotretinoin that had occurred between January 1997 and December 2017 using the FDA Adverse Event Reporting System (FAERS), which receives reports from prescribers, consumers, and pharmaceutical manufacturers. While there could be many different classification terms for each individual, any number of adverse events reported by an individual was counted as one pregnancy. Ms. Tkachenko and colleagues classified abortions, pregnancies during contraception use, and pregnancy-related defects into separate subgroups for analysis.

From 1997 to 2017, there were 6,740 pregnancies among women (mean age, 24.6 years) during treatment with isotretinoin reported to FAERS, with 7 reports in 1997, and a peak of 768 pregnancies in 2006. Almost 70% (4,647) of the pregnancies were reported after iPledge was introduced. Between 2011 and 2017, there were 218-310 pregnancy reports each year.

Of the total number of pregnancy reports during the study period, 1,896 were abortions (28.1% of the total); 10.9% of the total number of pregnancy reports were spontaneous abortions (733). The number of abortions peaked in 2008, with 291 reports, of which 85% were therapeutic abortions. Also peaking in 2008 was the number of reports of pregnancies while taking a contraceptive (64). After 2008, pregnancies and abortions dropped.

Fetal defects peaked in 2000, with 34 cases reported, and dropped to 4 or fewer reports annually after 2008.

"Our findings demonstrate that reports of pregnancy among women taking isotretinoin are concentrated among those aged 20 to 29 years, peaked in 2006, and have been consistent since 2011," the authors wrote.

Limitations of the study, they noted, include limitations of FAERS data and possible reporting fatigue among doctors and patients. The total number of isotretinoin courses prescribed to this patient population is also unknown, which affected their ability to determine the true rate of pregnancy-related adverse events, they noted.

The other authors for this study were from Harvard Medical School and the departments of dermatology at Brigham and Women's Hospital, both in Boston, as well as the University of Pennsylvania, Philadelphia. One author reported support from an award by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health and salary support from a Pfizer Fellowship in Dermatology Patient Oriented Research grant to the trustees of the University of Pennsylvania. The other authors reported no relevant conflicts of interest.

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SOURCE: Tkachenko E et al. JAMA Dermatol. 2019. doi: 10.1001/jamadermatol.2019.1388.

Commentary by Dr. Baldwin / iPLEDGE has been a bone of contention among dermatologists since we were introduced to it a year before its inception in 2006. Cumbersome at best, it resulted in a large increase in office cost and time expenditure and led to a reduction in prescriptions written for women with severe acne. What could not be denied was that pregnancy rates on isotretinoin had increased dramatically over the final years of the SMART program and something needed to change or isotretinoin was going to be taken off the market.

So now we hear that, despite our hard work in making iPLEDGE work, pregnancy numbers remained persistently high during 2006-2011, have dropped since then, but there were still 218-310 pregnancies per year. Presumably, iPLEDGE can't take credit for the improvement since 2011 as it wouldn't have taken 5 years for pregnancy numbers to decline. Whether it is because of improved U.S. pregnancy statistics in teens or reporting fatigue on the part of providers is unclear. Ultimately, the reason behind these trends matters little since fetal exposure is still at unacceptable levels. (What would we define as "acceptable"?)

Where is the failing? Is it the iPLEDGE system? It is hard to imagine a more stringent program, and I'm not sure that providers can cope with a more complicated system and still be willing to prescribe. Does the problem lie with our patients who are not telling us the truth? (A total of 64 patients got pregnant while on contraception – highly unlikely on two forms of birth control.) We're also missing some data – how many "abstinent" patients became pregnant? It may be that without our direct presence in the bedroom, we can't do any better than 250 pregnancies a year. It may be the price of doing isotretinoin business. Now we have to decide if it is acceptable.

Studies add clarity to *Demodex*, coffee link

IDENTIFYING ROSACEA TRIGGERS HAS BEEN DIFFICULT

By Elizabeth Mechcatie

EXPERT ANALYSIS FROM SDEF HAWAII DERMATOLOGY SEMINAR

LAHAINA, HAWAII – Recent data on the roles of caffeinated coffee and two types of *Demodex* species play in rosacea were discussed by Linda Stein Gold, MD, at the Hawaii Dermatology Seminar provided by Global Academy for Medical Education/Skin Disease Education Foundation.

As far as rosacea triggers, the role of coffee has been difficult to determine, according to Dr. Stein Gold, director of dermatology research at the Henry Ford Health System in Detroit.

"We know that caffeine can vasoconstrict; it also has anti-inflammatory properties so ... that might help rosacea," while the heat from a hot cup of coffee may cause vasodilation "and make rosacea worse," she noted.

But a recent study of data from the Nurses' Health Study II that evaluated intake of coffee, tea, soda, and chocolate every 4 years in over 82,000 women shed some light on the role coffee may play (JAMA Dermatol. 2018 Dec 1;154[12]:1394-400). There were almost 5,000 cases of physician-diagnosed rosacea in the cohort. When the investigators looked at caffeinated coffee consumption, "the more caffeine and the more coffee they drank each day, the more likely it was for them not to have rosacea," she said.

Those who consumed four or more servings of caffeinated coffee a day had a significantly lower risk of rosacea, compared with those who consumed one or fewer servings per month (hazard ratio, 0.77; 95% confidence interval, 0.69-0.87; *P* less than .001).

But there was no significant association with decaffeinated coffee or with edibles that contained caffeine such as tea, soda, and chocolate, "so something about caffeinated coffee seems to be protective for the development of rosacea," Dr. Stein Gold said.

Demodex mites

A few years ago, "we really didn't think much of *Demodex*, but now we know *Demodex* tends to be a key player" in people with rosacea, Dr. Stein Gold said.

In adults, the colonization rate of *Demodex* ranges from 70% to 100%, but the skin of people with rosacea have a particularly high density of *Demodex*: About 35%-50% of patients with rosacea have an increased *Demodex* load above 5 mites per cm^2, as measured with a standard skin surface biopsy, she noted. The density of *Demodex* in the skin of patients with rosacea has been measured at sixfold higher, compared with age-matched controls.

There also are two different *Demodex* species: *Demodex folliculorum*, which are longer, and *Demodex brevis*, which are short, and there is evidence that each "may cause an individual reaction," Dr. Stein Gold said.

She referred to a study that found a difference in the *Demodex* population in patients with highly inflammatory disease with a high level of *Demodex*, mild rosacea patients who did not have a lot of *Demodex*, and people with no rosacea (Dermatol Reports. 2019 Jan 23;11[1]:7675).

"Those people who had really severe, inflammatory rosacea had *Demodex folliculorum*," and the patients with the more mild disease or those with clear skin had *Demodex brevis*, she said, so "different species of *Demodex* might cause a different inflammatory reaction within individual rosacea patients."

Dr. Stein Gold reported that she has served as a consultant, investigator, or speaker for Galderma, Dermira, Foamix Pharmaceuticals, Valeant (now Bausch Health), Allergan, Actavis, and Roche.

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Commentary by Dr. Baldwin / Triggers for rosacea are myriad and individual. Not everyone has a trigger, but it is crucial to ask the appropriate questions to ascertain whether environmental factors contribute to the signs and symptoms of the individual patient. Avoidance of triggers, if possible, can result in disease improvement. The problem is that many triggers are not avoidable, or avoidance interferes with quality of life.

The most common triggers, according to an National Rosacea Society survey, include factors that the patient can and cannot control. Sun exposure is No. 1. Consumption of alcohol, spicy foods, hot baths, hot drinks, and use of skin care products are other triggers that are in the patient's control. Emotional stress (No. 2), hot weather, exercise, wind, and cold weather are largely uncontrollable variables. Although a patient can avoid the beach and ski slopes, this may affect their quality of life. Many patients report a worsening of erythema with exercise, but avoidance has negative health implications. Our patients are faced with some difficult decisions.

Hot beverages have long been a source of discussion as rosacea triggers. What makes them a trigger? Is it the heat of the beverage or the composition of the product? Caffeine causes vasoconstriction, and we could propose that it would make rosacea better, but vasodilation from the heat might make it worse. In this study, hot coffee consumption was associated with an improvement in rosacea. Decaffeinated coffee did not provide the same benefit suggesting that caffeine was protective, but other consumable sources of caffeine (chocolate, tea, soda) were not associated with improvement. Seems like an obvious next step to see what happens with iced coffee.

Unfortunately, this study has made the waters muddier than ever. For now, the take-home message seems to be that coffee consumption is a good thing, but for me, this doesn't change patient management. Trigger factors are highly individual, and regardless of study results, it always boils down to asking the patient what factors trigger their disease.

Often, a patient with combination disease is bothered more by one aspect than another. Many have a preference for oral or topical medication, and some patients are more side-effect averse than others. Branded products and physical modalities may not be covered by insurance and can be quite costly. By combining phenotype-directed recommendations with patient preference, an ideal treatment plan can be instituted that is truly individualized.

Benzyl benzoate–based topical reduced *Demodex*

STUDY EVALUATED PATIENTS WITH ROSACEA AND THOSE WITH DEMODICOSIS ONLY

By Michele G. Sullivan
FROM JEADV

Daily treatment with benzyl benzoate (BB) cream reduced *Demodex* densities in patients with and without rosacea, and was associated with improvement in clinical signs, according to F.M.N. Forton, MD, of the Dermatology Clinic, Brussels, and his coauthor in the Journal of the European Academy of Dermatology and Venereology.

The retrospective study comprised 394 patients treated between 2002 and 2010; 117 of them had rosacea with papulopustules and the remainder only demodicosis. Their mean age was 49 years; most were women. They had been treated with one of three doses of BB cream with crotamiton 10% cream: crotamiton applied in the morning, and BB 12% plus crotamiton in the evening; BB 12% plus crotamiton applied twice daily; and BB 20%-24% plus crotamiton applied once in the evening. *Demodex* densities (Dds) were measured with two consecutive standardized skin surface biopsies and deep biopsies at baseline and follow-up. Symptoms were measured with an investigator global assessment (IGA).

The authors said they had previously found that BB had acaricidal effects on *Demodex*, as did crotamiton "to a lesser extent," but that the two treatments have not been well studied. They also referred to the increasing evidence that *Demodex* has a role in papulopustular rosacea, and that ivermectin, which is acaricidal, is recommended for topical treatment of papulopustular rosacea.

In the study, a mean of 2.7 months after starting treatment, mean Dds were significantly lower for the entire cohort, decreasing by 72.4% (plus or minus 2.6%) from baseline. Dds had normalized in 35% of patients, and in 31% of patients, symptoms had cleared.

Treatment was considered effective in 46% of patients and curative in 20%. Men responded slightly better, with clearance in 34% vs. 20% of women. The two regimens using the higher dose of BB were more effective than those using the lower dose and were associated with better compliance. Compliance overall was 77%.

After a mean of nearly 3 months of treatment, "topical application of BB (with crotamiton) was effective at reducing Dds and clearing clinical symptoms, not only in demodicosis but also in rosacea with papulopustules, indirectly supporting a key role of the mite in the pathophysiology of rosacea," the authors concluded.

Neither of these products are approved in the United States for treating rosacea.

Dr. Forton disclosed that he occasionally works as a consultant for Galderma; the second author had no disclosures. The study had no funding source.

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SOURCE: Forton FMN et al. J Eur Acad Dermatol Venereol. 2019 Sep 7. doi: 10.1111/jdv.15938.

Commentary by Dr. Baldwin / Rosacea is a chronic inflammatory disorder with an upregulated and dysregulated innate immune system prone to excessive inflammation and vasodilation, coupled with neurogenic dysregulation and extrinsic triggers and exacerbating factors. That is a fancy way of saying that the exact pathophysiology of rosacea is unknown but is complicated and multifactorial. The literature has investigated the role of the microbiome in instigating or propagating the dysfunctional immune system in rosacea. Several cutaneous microbes have been implicated in the inflammatory response of rosacea, none more notably than *Demodex folliculorum* (but not its cousin *Demodex brevis* which is considered a saprophyte). This is complicated by the fact that *Demodex* often harbors a microbe within it, *Bacillus oleronius*, which may have the potential to stimulate an inflammatory response of its own. *Demodex* is a common inhabitant of the normal human facial hair follicle with colonization rates in adults as high as 70%-100%, but the load may be even higher in rosacea patients. One study showed a 5.7-fold higher demodex density in rosacea skin compared to healthy volunteers.

What remains to be seen is if this is cause or effect. Does the increased density of *Demodex* cause rosacea to occur? Or does rosacea skin, with its vasodilation and egress of proinflammatory mediators create an inviting milieu for the mites, which respond to happiness by multiplying? Does *Demodex* create the maladapted immune response or does it simply fuel an already primed system?

Proponents of the theory that *Demodex* causes rosacea point to the fact that drugs which are demodexicidal like benzyl-benzoate, crotamiton, and ivermectin result in clinical improvement. However, there are other explanations for this clinical benefit: ivermectin has numerous anti-inflammatory properties and crotamiton inhibits transient receptor potential vanilloid 4 (TRPV4) channels, which activates mast cells in patients with rosacea.

Perhaps an article states the entire conundrum in its title: "Are Demodex mites principal, conspirator, accomplice, witness or bystander in the cause of rosacea?" (Am J Clin Dermatol. 2015 Apr;16[2]:67-72). Clearly, evidence that *Demodex* causes rosacea has not met Koch's postulates by any stretch of the imagination: It is not present in every case of rosacea, it cannot be isolated from the host, and we do not know if the inoculation of *Demodex* into a healthy host will cause rosacea to occur. It may be a coconspirator, but we are far from concluding that it is causative.

National Rosacea Society

Bottom line: I don't care why these medications work, I'm just glad that they do.

Social media advice wanting in quality

MUCH OF THE ADVICE PATIENTS FOUND NOT ALIGNED WITH GUIDELINES

By Jennifer Smith
FROM PEDIATRIC DERMATOLOGY

A small survey suggests many patients consult social media for advice on acne treatment and follow recommendations that don't align with clinical guidelines.

Of the 130 patients surveyed, 45% consulted social media for advice on acne treatment, and 52% of those patients followed recommendations that don't correspond to American Academy of Dermatology guidelines. Most patients reported no improvement (40%) or minimal improvement (53%) in their acne after following advice from social media.

"These results suggest that dermatologists should inquire about social media acne treatment advice and directly address misinformation," wrote Ahmed Yousaf, of West Virginia University, Morgantown, and colleagues.

They conducted the survey of 130 patients treated for acne at West Virginia University. Most patients were female (60%), and a majority were adolescents (54%) or adults (44%). About half of the patients (51%) said their acne was moderate, 38% said it was severe, and 11% said it was mild.

Most patients said they consulted a medical professional for their first acne treatment (58%). However, 16% of patients said they first went to social media for advice, 26% said they consulted family or friends, and 10% took "other" steps as their first approach to acne treatment.

In all, 45% of patients consulted social media for acne treatment advice at some point. This includes 54% of women, 31% of men, 41% of adolescents, and 51% of adults. Social media consultation was more common among patients with severe (54%) acne than among those with mild (36%) or moderate (39%) acne.

The most common social media platforms used were YouTube and Instagram (58% each), followed by Pinterest (31%), Facebook (19%), Twitter (9%), Snapchat (7%), and Tumblr (3%). (Patients could select more than one social media platform.)

Roughly half (52%) of patients who consulted social media followed advice that does not align with AAD guidelines, 31% made changes that are recommended by the AAD, and 17% did not provide information on recommendations they followed.

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The social media advice patients followed included using over-the-counter products (81%), making dietary changes (40%), using self-made products (19%), taking supplements (16%), and making changes in exercise routines (7%). (Patients could select more than one treatment approach.)

Among the patients who followed social media advice, 40% said they saw no change in their acne, and 53% reported minimal improvement. "Only 7% of social media users reported significant improvement in their acne," Mr. Yousaf and colleagues wrote. "This may be due to less accurate content found on social media compared to other health care sources."

The authors acknowledged that the patients surveyed were recruited from a dermatology clinic. Therefore, these results "likely underestimate the percentage of patients who improve from social media acne treatment advice and do not consult a medical professional."

Mr. Yousaf and colleagues did not disclose any conflicts of interest.

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SOURCE: Yousaf A et al. Pediatr Dermatol. 2020 Jan 15. doi: 10.1111/pde.14091.

Commentary by Dr. Baldwin / The impact of social media on the acquisition of health-related information is increasing daily. Unfortunately, there are much data that suggest that the quality of said information is indirectly proportional to its accessibility. The bulk of YouTube dermatology videos are commercial or promotional in nature and tend to suffer from bias and misinformation.

For acne in particular, the majority of available videos are authored by non–health care sources and are plagued by commercialism. In Yousaf et al., it was noted that 52% of posts went against American Academy of Dermatology recommendations and patient outcomes were overwhelmingly negative. Even more concerning is the underlying mental health impact. In this era of media-induced perfection, viewers are often compelled to alter their digital appearance. In a study of Instagram postings, it was found that 88.7% edited their photograph prior to posting. Of those, 64% edited out a skin lesion and of those, 88% edited out acne or acne scars (J Cosmet Dermatol. 2020 Apr 25. doi: 10.1111/jocd.13456).

So how is the average viewer supposed to identify high-level information in social media? If the current trend of inaccurate posts cannot be halted, then it is incumbent upon dermatologists to dilute the pool with quality. In a recent article in JAAD, Sierro and co-workers issued a call to arms to the dermatologic community to disseminate high-quality educational information in order to promote good skin health and to dispel the false and harmful information prevalent on social media (J Am Acad Dermatol. 2020 Mar 7. pii: S0190-9622[20]30364-9). In a response to this study, Guzman and Barbieri added that our posts should represent the full breadth of our specialty (J Am Acad Dermatol. 2020 Apr 20. pii: S0190-9622[20]30675-7). They noted that most dermatologist-generated posts are from women in metropolitan private practices specializing in cosmetic procedures. Content, therefore, is skewed away from those who need it most: dermatology patients with conditions where misinformation can lead to delay in diagnosis and exacerbation of disease. The AAD and JAAD Instagram posts are an excellent step in the right direction.

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