ACNE & ROSACEA

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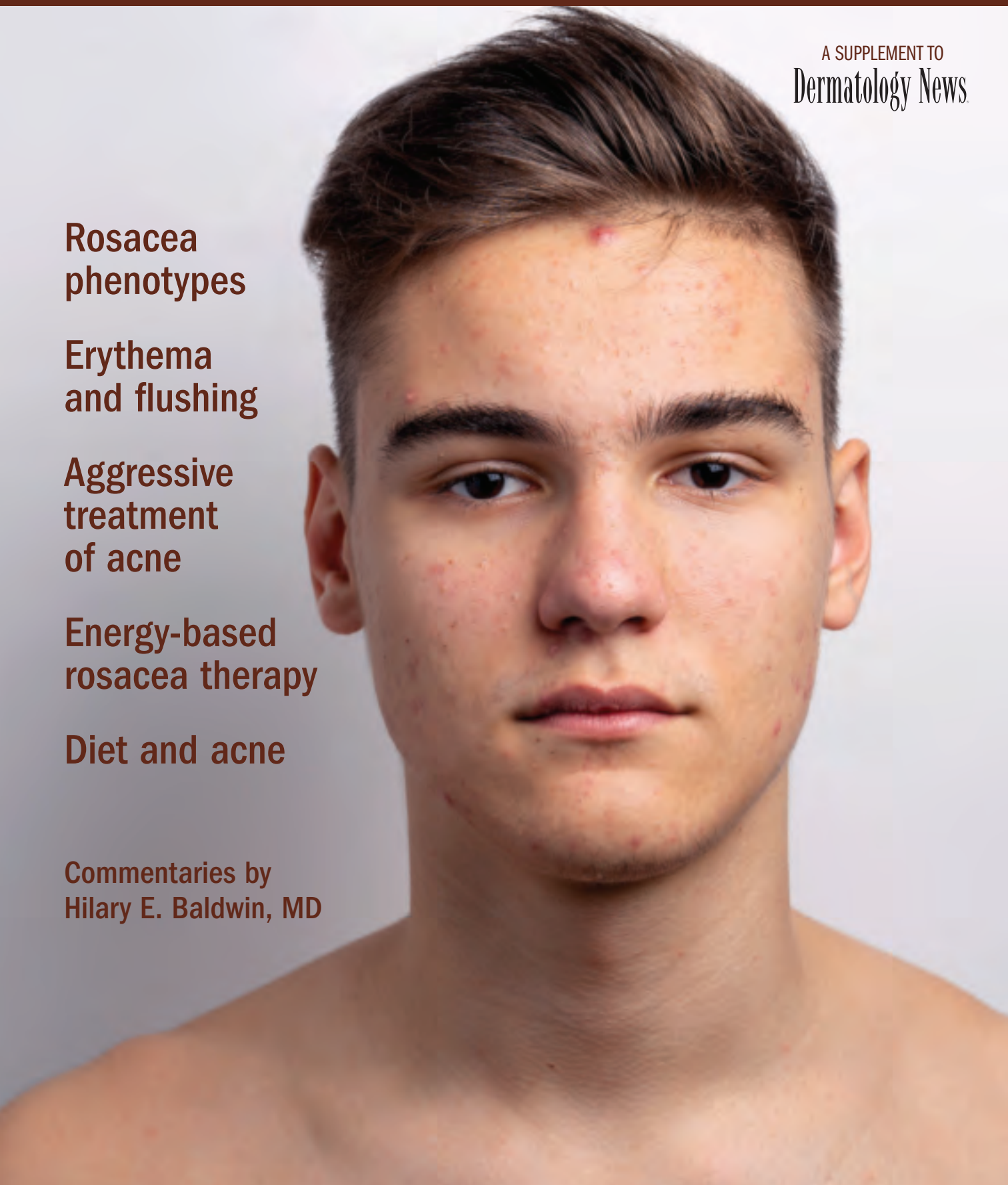

Rosacea phenotypes

Erythema and flushing

Aggressive treatment of acne

Energy-based rosacea therapy

Diet and acne

Commentaries by
Hilary E. Baldwin, MD

Dr. Hilary E. Baldwin

For the 2021 Acne & Rosacea Supplement, Hilary E. Baldwin, MD, provided commentaries on a selection of topics, published in Dermatology News over the past year, from published studies and meeting presentations.

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 speakers bureau of and is an adviser to Galderma, Ortho Dermatologics, Vyne Therapeutics, Almirall, and La Roche–Posay. She is also an adviser to Mayne Pharma, Cassiopea, Sol-Gel, and EPI Health.

Moving from subtypes to phenotypes is simplifying rosacea management

By Ted Bosworth
FROM COASTAL DERM

When a new phenotype approach to the diagnosis of rosacea was proposed 2 years ago, this simpler and more accurate method was accompanied by several corollary advantages, including a more rational approach to treatment and better methods of measuring treatment efficacy, according to an expert speaking at the annual Coastal Dermatology Symposium.

"By looking at rosacea in a more simple way – but a more accurate way – we are able to track what happens [to key features] over time," explained Jerry Tan, MD, of the University of Western Ontario, London.

The newer method of diagnosing rosacea, which relies on phenotyping rather than subtyping, focuses on symptoms and their clinical impact. With the previous method of subtyping, many rosacea patients failed to fit neatly into any of the four categories, producing confusion and diverting attention from troublesome symptoms.

"Rosacea patients often present with a range of features that span multiple subtypes or progress between them," Dr. Tan explained. The risk is not just a delay in diagnosis but also a failure to focus on symptoms patients find most bothersome.

The previous diagnostic criteria for rosacea, published in 2002, identified primary and secondary symptoms within its four subtypes (J Am Acad Dermatol. 2002 Apr;46[4]:584-7). The new diagnostic criteria, endorsed by the National Rosacea Society and published in 2018, rely on phenotypes defined by diagnostic, major, and minor symptoms (J Am Acad Dermatol. 2018 Jan;78[1]:148-55). Unlike the four previous subtypes, which were erythematotelangiectatic, papulopustular, phymatous, and ocular, the phenotypes facilitate diagnosis in patients with mixed features.

By replacing "the old thought process of subtyping" with a newer focus on phenotypes, the updated criteria were "aimed toward accuracy, simplicity, and practicality," Dr. Tan said.

Moreover, without squeezing patients into subgroups where they do not neatly fit, the new criteria draw attention to the specific symptoms that bring patients to the clinician.

The phenotype approach to treatment strategies was reflected in a systematic review of treatments based on phenotypes that was published in 2019, not long after the new classification system

Continued on page 5 ▶

Dermatology News

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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 20, 2020. **4.** Data on file.

Ortho Dermatologics

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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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▶ *Continued from page 2*

became available (Br J Dermatol. 2019 Jul;181[1]:65-79). In this review, coauthored by Dr. Tan, the GRADE certainty-of-evidence approach was employed to identify effective therapies, matching specific symptoms with specific therapies such as low-dose isotretinoin for papules or omega-3 fatty acids for dry eyes.

Dr. Tan also described a method of documenting the severity of major and minor symptoms at each visit, based on a patient-centric approach that emphasizes control of key symptoms. With this method, called a rosacea patient tracker, patients and physicians can determine whether therapies are effective against the signs and symptoms of disease that they find most burdensome, according to Dr. Tan, who was the first author of an article he cited as a reference to this phenotype-based methodology (Br J Dermatol. 2018 Sep;179[3]:741-6).

Overall, the phenotype approach to rosacea "rationalizes treatment," he said.

Specifically, the heterogeneity of symptoms in rosacea is mirrored in the heterogeneity of underlying pathophysiology. According to Dr. Tan, the upregulation of cytokines for inflammation, of angiogenic pathways for vascular symptoms, and of matrix metalloproteinases for tissue remodeling are all implicated in rosacea but drive different types of symptoms. While appropriate skin care and efforts to identify and minimize symptom triggers is appropriate for all patients, phenotypes provide a guide to the most appropriate therapies.

"The move to the phenotype approach is hopefully simpler, more accurate, and more relevant."

He said he hopes that the focus on phenotypes will draw attention to differences in these pathophysiological mechanisms. According to Dr. Tan, evaluating rosacea from the perspective of phenotypes has represented an important paradigm shift that extends beyond diagnosis.

"The move to the phenotype approach is hopefully simpler, more accurate, and more relevant," Dr. Tan said.

This same approach has been advocated by others, including Esther J. van Zurren, MD, professor of dermatology at Leiden University Medical Centre in the Netherlands, and the lead author of the 2018 systematic review article discussed by Dr. Tan. In this review article on the phenotype approach, specific strategies were recommended for specific symptoms on the basis of grading by an international group of experts that included Dr. Tan, a coauthor.

"These strategies should be directed toward achieving improvements in general well-being by targeting those aspects most bothersome to the patient," the article advises. Like Dr. Tan, Dr. van Zurren considers this phenotype-based approach to diagnosis and treatment to be a meaningful clinical advance over the guidelines published in 2002.

"Management strategies for people with rosacea should include phenotype-based treatments," she agreed, adding that specific choices should be made on the basis of these phenotypes "instead of the previous subtype classification."

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COMMENTARY BY DR. BALDWIN: How often is a new concept both more accurate and easier to implement? Such is the case with the changing paradigm for rosacea classification. Over the past 5 years, several expert and consensus groups have recommended the abandonment of the subtype classification of rosacea first published in 2002. At that time, rosacea was viewed as a single entity and new therapies purporting to improve disease did not routinely identify whether improvement was in erythema, papules or pustules, or other rosacea characteristics. For the first time, rosacea patients were categorized as having papulopustular, erythematotelangiectatic, phymatous, or ocular disease, and therapies were more clearly delineated.

Although it served its purpose at the time of its introduction, the subtype classification required clinicians and investigators to squeeze patients into a single category. As practitioners, we recognize that few patients have only one characteristic of rosacea; rather, most have multiple findings. Additionally, patient symptomatology was omitted from the subtype classification.

Specifying phenotypic characteristics of a patient's rosacea is considerably simpler than subtype classification. In essence, it asks us to consider, separately, the presence and severity of inflammatory lesions, background erythema, phymatous changes, telangiectasias, and ocular signs, and to document the patient's history of flushing, itch/pain, and ocular symptoms. This has several advantages. First, in clinical trials, we more clearly define the patients enrolled. Secondly, in clinical settings, we can track therapeutic improvement over time. Thirdly, it reminds us to evaluate each manifestation of disease separately when devising a therapeutic approach. Lastly, it simplifies the consultation as we discuss each aspect of disease with the patient to devise an overall treatment plan.

Treat acne aggressively upfront, expert advises

By Doug Brunk
FROM PEDIATRIC DERMATOLOGY 2020

In the opinion of Andrea L. Zaenglein, MD, the initial assessment of patients who present with acne should include five quick steps.

First, determine the types of lesions they have. "Do they have comedones, papules/pustules, and nodules present?" she asked during the Pediatric Dermatology 2020: Best Practices and Innovations Conference. Second, quantify the number of lesions that they have. Is it few? Several? Many? Third, determine the extent of their acne. "Is it limited to half the face, or is it generalized to the face, back, chest, and shoulders?" added Dr. Zaenglein, professor of dermatology and pediatrics at Penn State University, Hershey.

Fourth, identify postinflammatory changes such as erythema, hyperpigmentation, and scarring "because that's going to influence your management," she said. "Finally, you want to give a quick investigative global assessment of the acne severity where you quantify them as being clear, almost clear, mild, moderate, or severe. You want to do this with each patient at every visit so you can determine what their initial treatment's going to be and what their management going forward is going to be."

According to Dr. Zaenglein, the best acne treatments are based on the pathogenesis of the skin condition and trying to target as many pathogenic factors as possible. The four main pathogenic factors in acne include hyperkeratinization, increased sebum production, cutibacterium, and inflammation. "This is not a stepwise process; there's an interplay between all of those factors," she said. "All acne is inflammatory, but each of the treatments we have target specific factors. Retinoids target hyperkeratinization and inflammation, whereas the hormonal therapies will address decreased sebum production. Antimicrobial agents like benzoyl peroxide and antibiotics will work to decrease cutibacterium acnes. All of these are influenced by the exposome. This includes your genetics, external factors like pollution, or changes in, seasons that can affect your skin and the severity of your acne." A state of hyperandrogenism, she added, "can definitely increase acne" and is seen in patients with polycystic ovary syndrome.

For patients with mild acne, initial treatment should consist of a topical retinoid and, almost always, benzoyl peroxide, "unless it's a pure comedonal form of acne," Dr. Zaenglein said. She recommended using the combination of a topical retinoid and benzoyl peroxide, noting that, while it used to be difficult to find benzoyl peroxide, "nowadays there are numerous manufacturers and different formulations of benzoyl peroxide. We also have over-the-counter adapalene now, which is great. So, now we have a complete routine for patients with adapalene and benzoyl peroxide that you can combine together in a cost-effective way."

If the initial regimen fails to improve the patient's mild acne, a second-line treatment would be to change the retinoid and continue on the existing benzoyl peroxide formulation or to add dapsone gel if the patient is experiencing skin irritation. The four retinoids currently available include adapalene, tretinoin, tazarotene, and trifarotene. "These normalize keratinocyte

COMMENTARY BY DR. BALDWIN: Should we be the turtle or the hare when it comes to acne therapy? Clearly, since acne is a chronic disease, treatment will need to be continuous and lengthy. I have often heard experts refer to it as a marathon, not a sprint. But that doesn't mean that we can't or shouldn't, aim for a jackrabbit start. What are the relative benefits and risks of an aggressive early approach?

Aggressive starts generally require multiple medications. As Dr. Zaenglein discussed in her lecture, acne is best treated from several directions simultaneously, striving to reduce *Cutibacterium acnes*, follicular hyperkeratinization, sebum production, and inflammation whenever possible. Isotretinoin is the only drug we have that addresses all four factors as monotherapy, but it obviously is not appropriate for every patient. Although more effective, multiple medications means more copays and the possibility of reduced compliance. But patients who can pull it off reap the rewards.

Aggressive therapy can mean the increased potential for side effects. Most of our more efficacious drugs have higher side-effect profiles, although careful patient counseling can overcome this hurdle. Multiple medications may mean multiple side effects that require discussion. This brings us to another consequence of aggressive therapy: More time will need to be spent by providers/staff in education, prior authorizations, and patient callbacks. Frankly, shame on us if this stops us from doing what is right for our patients, but it undeniably affects treatment choices.

Aggressive therapy generally means more rapid response. This correlates with improved compliance as patients who see improvement are encouraged to continue their products on a regular basis. Lastly, early response has been shown to decrease the incidence and severity of scarring (Clin Exp Dermatol. 1994 Jul;19[4]:303-8).

Personally, I think it's a no-brainer. I'm with Dr. Zaenglein: Early and aggressive therapy is the best approach for acne. I'm a hare every time.

differentiation, reduce keratinocyte proliferation, and decrease expression of inflammatory markers," Dr. Zaenglein noted. "They also prevent scarring. Adapalene is considered to be the most tolerable, whereas tazarotene may have an edge on efficacy. There's a lot of overlap; head-to-head studies may not always match them up exactly, but generally this is how it's considered. Picking the right retinoid for your patient based on efficacy and tolerability is most important."

The newest topical retinoid, trifarotene 50 mcg/g cream, is a fourth-generation retinoid that is retinoic acid receptor gamma selective. Pivotal trials were conducted in patients aged 9 years and older with moderate facial and truncal acne. With monotherapy, there was a success rate of 36% at 12 weeks and 60% at 52 weeks, based on the Investigator's Global Assessment. Another newcomer, tazarotene 0.045% lotion, is a third-generation retinoid which is retinoic acid receptor alpha beta gamma selective. It's approved for moderate to severe facial acne in patients 9 years and older.

To optimize tolerance to retinoids, Dr. Zaenglein asks patients about their typical skin care regimen. "I ask them what they're washing their face with," she said. "Are they using apricot scrubs or harsh cleansers? Make sure they're applying it to the entire face and not spot-treating. You get less irritation when it's applied to dry skin, so you can recommend that. Make sure that they use a bland unscented moisturizer in the morning and apply it over top of their retinoid. I always warn them that irritation usually peaks at about 2 weeks. If they can power through, the irritation will improve with continued use."

To optimize adherence to retinoids, she asks patients how many nights per week they apply it. If they are using it all 7 nights, "they're good at using it," she said. "If they say 3 nights, then they need to work on getting it on more frequently."

Topical dapsone gel (5% and 7.5%) is mainly used for patients with papular-pustular acne. "Its mechanism of action for acne is not known, but presumptively it's anti-inflammatory," Dr. Zaenglein said. "It doesn't require G6PD [glucose-6-phosphate dehydrogenase] testing. It can cause some orange discoloration of your skin or fabrics if you use it with benzoyl peroxide, so you want to apply them at different times of the day. It's well tolerated. I tend to use it in patients who have problems tolerating any topical retinoid or any benzoyl peroxide but have mild to moderate acne."

For patients with moderate acne, consider combination therapy to target as many pathogenic factors as possible. "Use a topical retinoid plus benzoyl peroxide with or without a systemic antibiotic," Dr. Zaenglein advised. "I may give them an oral antibiotic if their acne is not responsive to the routine. But you wouldn't want to combine the systemic antibiotic with a topical antibiotic, like clindamycin with doxycycline, because you don't need two antibiotics. Make sure that you treat aggressively up front. It can take up to 3 months to see improvement. I counsel my patients that we'll rescue with the antibiotic and then we maintain, but we're going to stop that antibiotic after 3 months."

Systemic antibiotic options for acne include tetracyclines, doxycycline, minocycline, and sarecycline. "Tetracycline itself we don't use too much because you have to take it on an empty stomach, and availability is sometimes an issue," she said. "Primarily, we use doxycycline. You can take it with food, so that helps. The main side effects are gastrointestinal upset and photosensitivity. Alternately, you can use minocycline, which is also okay to take with food. It does have more potentially worrisome side effects, including pseudotumor cerebri, blue pigmentation, autoimmune hepatitis, and DRESS [drug reaction with eosinophilia and systemic symptoms]."

Sarecycline is the first narrow spectrum tetracycline for acne, with fewer vestibular and phototoxic side effects, compared with other tetracyclines. "It also has less effect on the GI flora," Dr. Zaenglein said. "It's a good alternative, but it can be costly, so make sure to check the pricing for your patients." She does not use other antibiotics such as TMP/SMX, penicillins, or cephalosporins for acne patients. "The reason is, the tetracyclines are not only antibacterial, but they're anti-inflammatory," she explained. "They also are lipophilic, so they will penetrate into the sebaceous unit where the heart of the acne is."

For patients who don't want to take an oral antibiotic, consider minocycline 4% foam, which was studied in moderate to severe acne in patients aged 9 years and older. The pooled results from the three studies showed a 47% mean improvement in inflammatory acne, compared with 37% among those in the vehicle arm. "You wouldn't use this as monotherapy; you'd use this in combination with the topical retinoid and the benzoyl peroxide," Dr. Zaenglein said.

Most primary care providers do not prescribe isotretinoin for patients with severe acne, but they can start patients on triple therapy with a topical retinoid, benzoyl peroxide, and a systemic antibiotic at its full dose. "The efficacy of triple therapy in patients you would typically deem as isotretinoin worthy is actually pretty good," she said. "There have been several studies looking at this, and about 70%-80% of patients will respond to triple therapy, where they are no longer deemed isotretinoin candidates. They still may need to move on to isotretinoin, but they will be improved."

Dr. Zaenglein disclosed that she is a consultant for Cassiopea, Novartis, and Pfizer. She has also received grants or research support from AbbVie, Incyte, and Pfizer.

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Energy-based therapy plus oxymetazoline found safe for rosacea

By Caleb Rans, PHARMD
FROM LASERS IN SURGERY AND MEDICINE

Energy-based therapy with adjunctive oxymetazoline was safe and improved facial erythema for patients with moderate to severe facial erythema associated with rosacea, in a phase 4 study.

The open-label study included 46 patients with rosacea, with moderate to severe facial erythema, who received treatment with one of four energy-based devices: pulsed-dye laser Vbeam Perfecta (PDL-Vbeam), pulsed-dye laser Cynergy (PDL-Cynergy), intense pulsed-light therapy (IPL), or potassium titanyl phosphate laser (KTP laser), in combination with adjunctive oxymetazoline hydrochloride cream (1%). On days 3-27 and 31-56, oxymetazoline, an alpha1A adrenoceptor agonist, was applied once daily, while energy-based therapy was provided on day 1 and day 29 (Lasers Surg Med. 2021 Jan;53[1]:55-65).

The primary safety endpoints were the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events; the exploratory efficacy endpoint was the change in clinician erythema assessment (CEA) score from start of therapy measured over a 6-hour period post treatment.

Among 43 evaluable patients (who completed the study), CEA score was improved in 39 (90.7%) patients 6 hours post treatment on day 56 and in 30 (68.2%) patients pretreatment. On day 31, "one-grade or greater improvement was observed" in 26 (60.5%) patients before application of oxymetazoline and in 38 (88.4%) of patients 6 hours post treatment, reported Emil A. Tanghetti, MD, of the Center for Dermatology and Laser Surgery in Sacramento, and coauthors.

Overall, patient satisfaction increased over the course of the study, with 28 (65.1%) patients reporting they were satisfied or very satisfied with the treatment on day 56.

Among 46 patients who received at least one treat-

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COMMENTARY BY DR. BALDWIN: Central-facial erythema is a common finding in rosacea. In fact, in the most recent paper on the phenotypic categorization of rosacea, central facial erythema, along with the presence of phymas, is considered diagnostic of the disease (Br J Dermatol. 2017 Feb;176[2]:465-71). It always bears repeating that this type of erythema (I prefer the term background erythema) is a distinct entity apart from two other red facial rosacea findings: perilesional erythema and telangiectasias. Failure to make this distinction has led to considerable confusion in the past, particularly when ascribing efficacy – or lack thereof – to a therapeutic approach.

Perilesional erythema is the small circle of erythema that often surrounds papules and pustules. In patients with severe inflammatory disease, there can be such an abundance of perilesional erythematous circles that therapeutic reduction of the lesions is accompanied by an overall impression of improved erythema. However, there are no data demonstrating that patients with true background erythema improve with drugs intended for inflammatory disease.

Background erythema responds well to alpha-adrenergic agonists and energy-based therapy. Telangiectasias do not respond to any form of pharmacologic therapy. Since the vascular wall of these vessels is not completely surrounded by smooth muscle, the alpha-adrenergic agonists are not able to constrict the vessels or create clinical improvement. Energy-based therapies are currently our only therapeutic option.

Combining alpha-agonists and energy-based therapies makes a great deal of sense. The alpha-agonists cause temporary vasoconstriction that resolves as the drug is metabolized. Two such agents, brimonidine and oxymetazoline, have terminal half-lives of about 24 hours, and most patients have returned to "baseline" by the next day. In some patients, return to baseline is accompanied by a temporary worsening of erythema (I prefer the term rebound erythema). This appears to be more common with brimonidine than oxymetazoline, although there is no head-to-head study. Energy-based therapies produce a more durable, sometimes permanent, response after several treatments. However, they may be costly for the patient. Immediately following the treatment, there is considerable redness in the treated area. Although temporary, it is a cause for alarm and dissatisfaction for the patient.

So, what does the combination potentially bring to the table? Brimonidine had previously been shown to reduce postprocedure erythema (Lasers Surg Med. 2018 Dec;50[10]:1002-9). Before and between treatments, topical agonists can control erythema on a daily basis until the time they are no longer needed. The energy-based therapy will treat telangiectasias as well. In patients in whom both severe background erythema and telangiectasias are present, use of the alpha-agonists often results in such good resolution of erythema that the telangiectasias stand out in stark contrast. So, the patient enjoys the reduction in redness but is now bothered by the telangiectasias.

Lastly, alpha-agonists can be used intentionally prior to laser treatment of telangiectasias to make them more visible and easy to treat. Knowledge provided by Tanghetti et al. that we can safely use the two modalities together is a major advance.

Review finds evidence for beta-blockers for some rosacea symptoms

By Richard Mark Kirkner
FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

A systematic review of nine studies provided limited evidence that off-label oral nonselective beta-blockers can be an effective treatment for facial erythema and flushing in rosacea, while at the same time, underscoring the paucity of evidence supporting their use, investigators reported.

"The evidence was highest for carvedilol and propranolol, two nonselective beta-blockers," wrote Jade G.M. Logger, MD, of the department of dermatology, Radboud University Medical Center in Nijmegen, the Netherlands, and coauthors (J Am Acad Dermatol. 2020 Oct;83[4]:1088-97).

The systematic review included a case control study of 53,927 patients and an equal number of controls that evaluated beta-blockers in general (Br J Dermatol. 2014;171[1]:130-6), but the remaining studies and case reports included only 106 patients in total. The largest was a prospective cohort study of propranolol in 63 patients (J Am Acad Dermatol. 2012;67[3]:491-3).

The studies included patients with a history of failed therapies; only a small number of beta-blockers were evaluated. Outcomes in the studies varied widely, which ruled out doing a meta-analysis. "Erythema and flushing were assessed by using a wide spectrum of mostly subjective clinical and patient-based scores, and method standardization was often missing," the researchers stated.

"Most studies showed improved erythema and flushing after initiation of oral beta-blockers," they wrote.

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COMMENTARY BY DR. BALDWIN: Not all manifestations of rosacea are easily treated. We have an embarrassment of riches when choosing a medication for inflammatory lesions: The Food and Drug Administration–approved topical agents and subantibiotic dose doxycycline are highly effective. For vascular disease, the topical alpha-adrenergic agonists and laser and light therapy result in excellent responses. Energy-based therapies improve telangiectasias, and phymatous lesions can be eradicated with ablative techniques.

The one sign of rosacea over which we have the least therapeutic control is flushing and blushing. Behavioral approaches that call for avoidance of triggers are minimally effective and disruptive and often reduce patient quality of life. Taking aspirin and other NSAIDs, SSRIs, and clonidine, as well as chewing on ice cubes, have met with limited to no success. Over the years, beta-blockers have been reported in underpowered and poorly designed studies to be marginally effective while accompanied by significant side-effect profiles. In a recent systematic review of beta-blocker studies, nine studies were recognized by Logger and colleagues as having a modicum of merit, but the variety of outcome measures precluded a meta-analysis and usable clinical information. The evidence, such as it was, was highest for carvedilol and propranolol.

Recently, Abid and colleagues published an article suggesting that the long term use of antihypertensive drugs with vasodilatory mechanisms of actions might actually protect against vascular rosacea (J Am Acad Dermatol. 2021 Feb 9; S0190-9622[20]33243-6). This is not particularly surprising as many of the drugs that vasodilate centrally vasoconstrict peripherally. Beta-blockers, for example, cause vasodilation in the heart by binding to beta-1 receptors but constrict the cutaneous blood vessels after binding to beta-2 receptors. It is reasonable to propose that continuous reduction in vascular tone in the skin, such as that which might occur with daily use of a hypertensive agent, might affect background erythema in the skin over time. A larger study is needed to assess this preliminary finding and to see if the most elusive of our rosacea findings – flushing – is reduced.

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ment, five (10.9%) patients had one or more TEAEs (KTP laser, n = 1; PDL-Vbeam, n = 4), and four patients had one or more treatment-related TEAEs (PDL-Vbeam, n = 4). All TEAEs were considered mild or moderate. "Three (6.5%) patients experienced TEAEs related to oxymetazoline; all led to study discontinuation," the researchers reported.

The researchers acknowledged that a key limitation of the study was the use of multiple energy-based devices, delivered by different providers, which could have caused inconsistency in the results.

"Prospective clinical studies assessing the long-term safety and efficacy of combined treatment with oxymetazoline and energy-based therapies are needed," they concluded.

The manuscript was funded by oxymetazoline manufacturer Aclaris Therapeutics. Several authors disclosed being an investigator, consultant, and/or laser manufacturer. One author was an employee of Aclaris at the time of the study.

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High-fat, high-sugar diet may promote adult acne

By Heidi Splete

A diet higher in fat, sugar, and milk was associated with having acne in a cross-sectional study of approximately 24,000 adults in France.

Acne in adults has been associated with social, emotional, and psychological consequences similar to those found with chronic diseases such as asthma, arthritis, epilepsy, and diabetes, wrote Laetitia Penso, MSc, of the University of Paris in Bobigny, France, and colleagues.

Although acne patients may believe that eating certain foods exacerbates acne, data on the effects of nutrition on acne, including associations between acne and a high-glycemic diet, are limited and have produced conflicting results, they noted.

In their study, the researchers identified 24,452 adults who participated in the NutriNet-Santé study, an ongoing, web-based study in France. Approximately 75% of the participants were women, the average age was 57 years, and 46% reported past or current acne (JAMA Dermatol. 2020 Aug 1;156[8]:854-62).

Participants responded to an 11-item questionnaire between November 2008 and July 2019. Questions were related to the occurrence and diagnosis of acne, as well as medical history. Based on their acne status, participants were identified as falling into the categories of never acne, past acne, or current acne, and their dietary intake was assessed at baseline and every 6 months using three nonconsecutive 24-hour dietary records for 2 weekdays and 1 weekend day.

In an analysis, after adjustment for confounders, current acne was significantly associated with consumption of fatty and sugary foods (per portion, adjusted odds ratio, 1.54; $P = .01$), as well as with consumption of sugary drinks (per glass, aOR, 1.18; $P = .04$) and milk (per glass, aOR, 1.12; $P = .04$). In addition, carbohydrate intake and saturated fatty acid intake were significantly associated with current acne (aOR, 1.43; $P = .02$; and aOR, 3.90; $P = .048$, respectively).

Three dietary patterns accounted for 42% of the total variability, the researchers said. A healthy pattern of higher fruit, vegetable, and fish intake accounted for 18%; a fatty and sugary pattern of higher fat and sugar intake (including chocolate) accounted for 13%; and an animal product and cereal pattern of higher intake of meat, milk, and re-

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Treatment of facial erythema and flushing remains a clinical challenge, despite approved therapies for which poor response and reactivation are common. "Diminishing erythema and flushing in rosacea is challenging because it hardly responds to conventional anti-inflammatory treatment," they noted.

"The study adds no new evidence to support the use of beta-blockers," Diane M. Thiboutot, MD, professor of dermatology at Penn State University, Hershey, said in an interview. "As the authors point out, the nine studies reviewed were of low quality with a variety of outcome measures that precluded generation of a meta-analysis, which would have represented new information."

Dr. Thiboutot is lead author of a 2019 update of management options for rosacea published by the National Rosacea Society Expert Committee (J Am Acad Dermatol. 2020; Jun;82[6]:1501-10). Beta blockers are among the drugs that are sometimes prescribed off label to help rosacea-associated flushing, along with nonsteroidal anti-inflammatory drugs, antihistamines, and clonidine, according to the update.

Dr. Logger and coauthors noted that beta-blockers come with risks and can aggravate asthma and psoriasis and are contraindicated in patients with heart failure, cardiogenic shock, and other cardiovascular diseases, along with hyperactive airway and Raynaud's disease. "It is important to monitor patients for adverse effects, especially blood pressure and heart rate," they stated. Carvedilol and propranolol may have more antioxidant and anti-inflammatory properties than other nonselective beta-blockers that may curtail rosacea manifestations, they wrote.

They called for large, prospective clinical trials to more accurately assess the efficacy of beta-blockers in rosacea patients. "Researchers should further focus on the determination of the optimal dosage, treatment duration, and long-term therapeutic effects for adequate treatment of erythema and flushing in rosacea," they said.

Getting those trials is challenging, Dr. Thiboutot said. Nonetheless, the studies would be welcome, she said. "If standardized outcome measures for facial erythema were to be developed, a study would be more feasible."

Dr. Logger disclosed financial relationships with Galderma, AbbVie, Novartis, Janssen, and LEO Pharma. One author disclosed conducting clinical trials for AbbVie and Novartis. The third author disclosed relationships with Galderma, Cutanea Life Sciences, AbbVie, Novartis, and Janssen, with fees paid to his institution. Dr. Thiboutot disclosed a financial relationship with Galderma.

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fined cereals accounted for 11%, they explained.

"The results of our study appear to support the hypothesis that the Western diet (rich in animal products and fatty and sugary foods) is associated with the presence of acne in adulthood," the researchers concluded. Possible explanations for the findings include the effects of a high–glycemic load diet on circulating IGF-1 and insulin, which ultimately increases both oxidative stress and inflammation that promotes the development of acne, they noted.

The study findings were limited by several factors including the use of relatively homogeneous younger and female patient population and the reliance on self-reported acne, as well as the observational design, which did not allow for identification of direct, causal associations between diet and acne, the researchers noted. Larger studies are needed to examine the relationship between diet and adult acne to inform prevention and treatment, they wrote.

"Much of the previous literature on the role of diet in acne has focused on the association of milk consumption and high glycemic-load diet with acne," John S. Barbieri, MD, of the department of dermatology at the University of Pennsylvania, Philadelphia, wrote in an accompanying editorial (JAMA Dermatol. 2020 Aug 1;156[8]:841-3).

Dr. Barbieri acknowledged the inability to make causal associations given the study design and noted that dietary interventions should be implemented with caution because of the potential for other effects such as reduced calcium or vitamin D.

"Nevertheless, given the potential overall health benefits of a healthy or low–glycemic load diet, and two small trials supporting its effectiveness in acne, a low glycemic-load diet is a reasonable recommendation for patients looking for dietary modifications that may improve their acne," he said.

"A low glycemic-load diet is a reasonable recommendation for patients looking for dietary modifications."

Dr. Barbieri said that he was encouraged to see that the study findings reflected previous research identifying an association between acne and high-glycemic load foods, as well as milk consumption, but he emphasized that more research is needed before general recommendations about diet and acne can be made.

"Trials are needed to evaluate whether dietary interventions can improve or prevent acne and how the effect size of such interventions compares with other standard treatment modalities," he emphasized.

The study received no outside funding. The researchers had no financial conflicts to disclose. Dr. Barbieri disclosed support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health and from a Pfizer Fellowship grant to the Trustees of the University of Pennsylvania.

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COMMENTARY BY DR. BALDWIN: I spend a lot of time with my first-time acne patients. We discuss the anticipated timeline of acne, general pathophysiology, and the role of medications/procedures, as well as reasonable expectations for improvement. Together, we arrive at a therapeutic regimen that fits their lifestyle, is affordable, and is in agreement with their disease severity, comfort level, and cultural belief systems. The one subject I never bring up (and fervently hope they don't either), is diet.

My rationale for this omission has been that I do not have definitive answers or data-based recommendations. If I don't know the answer, why would I pose the question? I have found it to be a pointless, time-consuming rabbit hole. If I do it well, the discussion is complicated and murky, and I end up recommending a low–glycemic index diet. If I do it poorly, the patient may be unsatisfied, and I end up recommending a low–glycemic index diet. Not because I'm convinced that it would make a difference, but because, in the absence of data, I have felt most comfortable defaulting to a healthy diet – so does the American Heart Association and the Centers for Disease Control and Prevention. Who needs me to add my two cents?

The NutriNet-Santé study adds additional, sorely needed data to help frame our discussion with our patients. The finding that dairy consumption and high–glycemic diet were associated with acne mirrors prior small trials and lends credence to the outcome. However, the authors and commentators all agree, larger trials are needed to assess causality and to determine if dietary interventions will make a meaningful clinical impact. I fear that this is easier said than done. A prospective trial would need to be very large and of long duration; acne doesn't alter its course rapidly. Without pharmaceutical support, who will pay for this expensive trial? Participants in the NutriNet-Santé trial were older women with acne, a group that can be relied upon for compliant behavior. As anyone who has ever tried to switch to a healthier diet or lose weight can attest, behavioral changes are hard-won and short-lived. I find it hard to imagine that a sufficiently large group of teenagers will adhere to a sufficiently low–glycemic index diet for a sufficiently long period of time to create a sufficiently measurable difference in acne. That last piece of pizza calls ...

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