A-8. This 61-year-old patient shown with severe atopic dermatitis changed the way one expert thinks about treating moderate-to-severe atopic dermatitis in adults.

Photos: Ted Rosen, M.D.

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Difficult-to-treat AD lesson

LISETTE HILTON | Staff Correspondent

Ted Rosen, M.D., professor of dermatology at Baylor College of Medicine, Houston, Texas, says a 61-year-old patient changed the way he thinks about treating moderate-to-severe atopic dermatitis in adults.

The woman sought treatment with Dr. Rosen more than a year ago for an atopic dermatitis flair he describes as horrible.

“It wasn’t just her neck. It was on her antecubital fossa, popliteal fosssa, face…. About the only place that wasn’t horrific and was just mild was her trunk,” Dr. Rosen says.

A little history: The patient had allergic rhinitis and asthma during her life but both self-resolved. She had mild atopic dermatitis as an infant but it worsened as she aged, especially during adolescence.

“She literally had not had clear skin since before high school, age 12,” he says.

The patient relocated to Houston, where Dr. Rosen says the heat, humidity and pollution would only serve to make her skin itchier—to the point that her ability to do even daily activities suffered.

She went through the normal medication

LESSON CONTINUES ON PAGE 86

Manage practice change

Drive innovation from the ground up

STEPHANIE STEPHENS | Staff Correspondent

Change is inevitable, says medical practice consultant, Debra Phairas, something frequently acknowledged by W. Edwards Deming, an engineer and management consultant she reveres.

“He said we must ‘improve constantly and forever,’ or get left behind. I believe that,” she says. Phairas, who is president of Practice & Liability Consultants, LLC, based in San Francisco, adds “doctors are usually more able to make changes in evidence-based medicine.”

But, they are not practicing medicine the same way they did 25 years ago, she says.

“Advances occur on the business side, too, and it’s necessary to keep up,” she adds.

MAKE CHANGE COMPREHENSIVE AND FUN
Take a hard look at your practice and apply the same strict standards all around. Consider every angle.

Your staff may need an up-to-date standard of care, but they also may need a good photocopier, along with new computers and software on a regular basis to do the best job, Phairas says.

CHANGE CONTINUES ON PAGE 80
FOR ADULTS WITH PLAQUE PSORIASIS

CHART A COURSE TO SYMPTOMATIC RELIEF

The efficacy of Class 1 halobetasol with safety proven for up to 8 weeks of dosing\(^1\)

A NEW POTENCY CLASS OF STEROID LOTION

\(^2\) PIVOTAL PHASE 3 TRIALS

POTENT TO SUPERPOTENT CLEARANCE\(^1\):

- **Continued results** 4 weeks post treatment\(^1\)
- **Significant symptomatic relief** as early as week 2\(^2\)
- **No increased epidermal atrophy** observed through 8 weeks of treatment\(^2\)

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, hypopigmentation and allergic contact dermatitis. Some local adverse reactions may be irreversible.

**STUDY RESULTS:** 36.5% of patients in trial 1 and 36.4% in trial 2 achieved treatment success\(^1\) at week 8 (primary endpoint) vs. 8.0% and 12.0% of patients with vehicle, respectively \(P=0.001\) in both trials\(^1\)

**STUDY DESIGN:** The safety and efficacy of BRYHALI Lotion were assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 430 adult patients with moderate-to-severe plaque psoriasis. Patients were treated with BRYHALI Lotion or vehicle lotion, applied once daily. Primary efficacy endpoint was treatment success evaluated at week 8. Secondary efficacy endpoint was treatment success evaluated at weeks 2, 4, 6, and 12 (6 weeks post treatment). Tertiary efficacy endpoint was a 2-grade improvement from baseline at each time point for the individual signs of psoriasis: erythema, plaque elevation, and scaling\(^2\).

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


**Indication**

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is a corticosteroid indicated for the topical treatment of plaque psoriasis in adults.

**Important Safety Information**

**Warnings and Precautions**

- BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.
- Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria.
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.
- Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.
- Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.
- Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.
- Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

**Adverse Reactions**

- The most common adverse reactions (≥1%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

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

Ortho Dermatologics

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DISCOVER MORE AT BRYHALI.COM
BRIEF SUMMARY OF PRESCRIBING INFORMATION
This brief summary does not include all the information needed to use BRYHALI safely and effectively. See full prescribing information for BRYHALI.

BRYHALI™ (halobetasol propionate) lotion, 0.01% for topical use
Initial U.S. Approval: 1990

INDICATIONS AND USAGE
BRYHALI™ (halobetasol propionate) Lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression
BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 19 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA). HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (15.8%) subjects at Week 8. All 3 subjects had normal HPA axis suppression test with discontinuation of treatment [see Clinical Pharmacology in full prescribing information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concurrent use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

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

Local Adverse Reactions
Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. These may be more likely with occlusive use, prolonged use, or use of higher potency corticosteroids, including BRYHALI. Some local adverse reactions may be irreversible.

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

Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

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

In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRYHALI (N=284)</th>
<th>Vehicle (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Application Site Dermatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

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

Lactation
Risk Summary
There are no data on the presence of halobetasol propionate or its metabolites in human milk; the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

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

Clinical Considerations
Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use
Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years have not been evaluated.

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

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

Geriatric Use
Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older. Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

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

Studies in rats following oral administration of halobetasol propionate at doses levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for:
Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:
Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
U.S. Patent Numbers: 6,517,847 and 8,809,307
BRYHALI is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.
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Based on 9652102 November 2018 BRY0032.USA.18
In this issue, you’ll find insight into coming trends in dermatology and aesthetics, as well as new possible targets in skin cancer treatment. You’ll also see practical guidance from experts and literature reviews on topics such as caring for foot dermatoses, onychomycosis, and hemangiomas, as well as managing reimbursement, employing telemedicine, marketing tactics and more. As always, we love your feedback. Talk to us at editor@dermatologytimes.com.

**Our Mission:** Provide practical analysis of recent studies, regulatory updates, techniques, devices and business solutions; and facilitate discussion to optimize practice and improve patient care.

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Cream and Ointment

240 g
Cream and Ointment

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*Prescriptions that may be reimbursed under federal or state healthcare program (including Medicaid and Medicare) are not eligible under this program. Additional restrictions may apply.
The need to expand OTC product knowledge

Dermatologists are experts in skin, hair and nail issues. Traditionally, dermatology textbooks and training have focused on diagnosis and prescription treatment of disease. This is the core of dermatology and should remain the primary goal of all residency programs.

However, much new and emerging useful knowledge is present in the area of over-the-counter (OTC) technologies. The high cost of prescription medications has driven many consumers to look for remedies in the OTC drug realm. Further, little attention is focused on skin disease prevention and the maintenance of skin health. These are areas where prescription medication may not be appropriate and OTC products become of primary importance. Do dermatologists possess the knowledge base to effectively use OTC products? I am not sure.

Do dermatologists understand the difference between soaps and syndets and how they might benefit or damage eczematous skin?

Do dermatologists understand the difference between a conditioning shampoo and a dandruff shampoo and their differing effects on seborrheic dermatitis?

Do dermatologists know whether a lotion containing ceramides or grapeseed oil is better for rosacea patients?

I am not sure.

OTC products are becoming increasingly complex with enhanced efficacy due to the tremendous explosion in raw materials available for formulation. The simplistic moisturizer made of petrolatum and mineral oil emulsified in water is no more. Moisturizers can be built to reduce transepidermal water loss to various levels, provide viscosities appropriate for various body areas, and deliver a variety of bioidentical materials to the skin surface. The OTC acne market is expanding with great rapidity based on the new small particle benzoyl peroxide that allows better skin coverage with lower concentrations. The Rx to OTC switch of adapalene also created unprecedented efficacy in the nonprescription acne market. Other previously prescription-only acne actives will undoubtedly consider making the switch.

One of the biggest obstacles to expanding the acceptance of review articles and textbook chapters on skin, hair and nail care technologies that are not OTC drugs is the lack of “evidence-based” information. Who is going to do a study to demonstrate that various detergents work?

How can you compare 40 different facial moisturizer formulations and determine which one works best?

How do you demonstrate which shampoo produces the least amount of dandruff?

Consumers do this every day in the marketplace based on their purchases. A product that does not work does not stay on the shelf for long. Consumers are the scientists and will buy one bottle, but will not buy a second, followed by the store discontinuing the offering. Want to know which products do not work? Look at the clearance aisle in the store!

Further, it is not possible to examine 40 facial moisturizers and determine which one is the best for all. Why are there 40 different facial moisturizers for sale? Because they all work for someone who purchases them. Why are there so many different botanical-containing cosmetic formulations? Because they all work for someone who purchases them. There is no one size fits all when it comes to skin, hair and nail care. Customization is the secret to success. With this in mind, evidence-based approaches do not work. Instead, dermatologists need to understand the mechanism of action for these ingredients.

I believe there is a need in dermatology training and beyond into practice to expand the understanding of OTC products. There should be at least one day in every training program devoted to OTC technologies. My brief survey indicates that at least 30% of patients seen in an average dermatology practice will ask one question about an OTC product or issue. The dermatologist should be confident in answering the question quickly and accurately. These common “door handle” questions require an expanded OTC understanding.

“ A product that does not work does not stay on the shelf for long. Consumers...will buy one bottle, but will not buy a second...”
Ortho Dermatologics

Investing in the Future of Dermatology

Through the leadership of Radhakrishnan (RK) Pillai, PhD, and his team, Ortho Dermatologics is working hard to create innovative solutions and fill its pipeline with quality products. As a researcher for the past 20 years, RK has collaborated with leading dermatologists, including having a long-standing relationship with Dr. Jonathan Weiss.

The connection between RK and Dr. Weiss stems from a common goal: providing patients with the best product options.

I see innovation in two ways. One is improving on existing compounds, and the other is creating brand new products and formulations.

Radhakrishnan (RK) Pillai, PhD, Vice President, Research and Development

Where does your passion for research and development stem from, and what impact does it have on the dermatology community?

RK Pillai: Research and development have always been my goal, and pharmaceuticals my passion. To me, dermatologic research was most appealing because of the associated challenge of creating formulations for skin that work on all parts of the body. Our pharmaceutical research is all about helping patients who have problems with their skin and getting them the best results possible.

Dr. Weiss: Research and development are necessary for making advancements that I can then offer my patients, and allow my practice to constantly evolve as disease states change. Without promoting advancements in dermatology, we would have no additional options to provide patients.

Why is formulation important in establishing a successful pipeline?

RK Pillai: When we think about treating a disease, we think about what formulation would best be suited for that specific disease. Formulation is also a science. We look at new chemicals, combinations, and classes of molecules. In doing so, we’re able to achieve more options for the products we are providing to dermatologists and patients.

Dr. Weiss: As a clinical dermatologist, I view formulation as absolutely key for our patients. Ortho Dermatologics and Dow Pharmaceuticals have been the formulation masters since the 1970s, able to accomplish things that couldn’t previously be done. As time has gone by, Ortho Dermatologics’ approach to formulation—and research and development as a whole—has made a huge difference in my career and helped deliver excellent results to generations of patients.

What stands out most to you about Ortho Dermatologics?

RK Pillai: It takes time to create a quality product, and our team understands that patience is required to see that to fruition, to understand what the community’s needs are, and ultimately, to provide quality products to dermatologists as their trusted source in the field.

Dr. Weiss: When I think about Ortho Dermatologics and what they’ve done, they’ve really stayed true to their core mission. The entire team at Ortho Dermatologics is passionate in bringing that mission to life, putting the community and patient needs first, and I think an important component of that is their commitment to research and development.

Watch Radhakrishnan (RK) Pillai, PhD, and Dr. Jonathan Weiss discuss more about the future of dermatology at www.ortho-dermatologics.com
I
novation is an expensive, arduous and long process. Partnerships are key for success. In drug development, industry relationships are close to essential. For medical devices, industry partnerships can be extremely helpful in navigating the expensive regulatory process. Even within health information technology, there is a strong and growing interest from traditional industry players to get involved in the deployment of software solutions and to generate scale.

Academic and industry collaborations are essential to bring together the critical capabilities and resources necessary to move innovations to the marketplace. Many physicians have collaborative relationships with industry through consulting, sponsored research programs, joint development agreements and technology development. Collaborations with industry offer new opportunities and challenges for physicians seeking intellectually stimulating side ventures. While physicians know medicine and they know science, they may not know business, which is why these collaborations can be essential.

Over the past several years, there has been a trend in industry to create innovation hubs to foster collaborations between physicians, scientists, engineers and industry. The hubs create a natural conduit to foster discussion and lend support to novices seeking to launch a product, device, software solution—or, really, the sky is the limit.

Academic and industry collaborations are essential to bring together the critical capabilities and resources necessary to move innovations to the marketplace. Many physicians have collaborative relationships with industry through consulting, sponsored research programs, joint development agreements and technology development. Collaborations with industry offer new opportunities and challenges for physicians seeking intellectually stimulating side ventures. While physicians know medicine and they know science, they may not know business, which is why these collaborations can be essential.

Here are few examples of innovation hubs:

- **LEO Science & Tech Hub (LEO Pharma):** The LEO Science & Tech Hub is a R&D innovation unit of LEO Pharma. They explore cutting-edge science and technology opportunities with relevance to dermatology. Their interests include non-invasive biomarkers, imaging technologies and artificial intelligence.

- **Johnson and Johnson Innovation, JLABS:** This group invites collaborations across the entire spectrum of pharmaceuticals, medical devices and consumer health. They offer mentorship, non-diluting grants and incubator space. Over the course of six years, companies incubated at JLABS have secured more than $1.6 billion in funding, 10 IPOs and 12 acquisitions. Dermatology remains a significant portfolio of J&J’s pharmaceutical subsidiary (Janssen) as well as its consumer health portfolio as makers of Neutrogena.

- **AlmirallShare:** The Spanish pharmaceutical company Almirall has established an open platform to encourage outside innovators to work with Almirall to develop new, innovative solutions for skin health. Their initial focus centers on inflammatory skin conditions such as rosacea, and acne.

- **Bayer LifeScience iHUB, Bayer Open Innovation:** Like Johnson & Johnson, Bayer AG is a massive organization with its own innovation program. Across their pharmaceuticals and consumer health divisions, there are opportunities for innovators to engage with Bayer on areas of shared interest.

- **L’Oréal’s Technology Incubator:** L’Oréal’s supports a technology incubator to engage with outside partnerships. This work has led to new devices such as UV sensors and smart combs.

Innovations centers open new doors to innovators or wannabe innovators who may need guidance with research, product development, regulatory hurdles and marketing.

**TIPS FOR COLLABORATION WITH INDUSTRY**

1. **MANAGE EXPECTATIONS:**
   These are large, complex organizations with an unknowable set of interests that change. You may have the greatest basal cell carcinoma drug candidate, but a company may simply be exiting skin oncology for strategic reasons. So, a “no” now may not be a “no” forever.

2. **HAVE A REALISTIC VIEW OF CONFIDENTIALITY:**
   The value you offer is your idea, so sharing what you are working on is a prerequisite to collaboration. File patents (even inexpensive provisional patents) and request confidentiality agreements, but do not let the fear of someone stealing your idea prevent you from identifying a critical partner.

3. **CLARITY IS KEY:**
   You may have a platform technology, but identifying one or two key beachheads really help your potential industry partners understand what you want to do and whether they are a good fit.
**Fast Results. Focused Delivery.**

Help your mild-to-moderate plaque psoriasis patients show their unexpected with the proven power of SERNIVO® Spray.

**Progress You Can See**

Improvement in psoriatic plaque on the knee over 28 days of treatment.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 14</th>
<th>Day 29</th>
</tr>
</thead>
</table>

Actual patient. Individual results may vary.

**Powerful Results**

Investigator’s Global Assessment of treatment success.

20.3% at day 15* vs. vehicle, 5%; P<.001 (n=538)³

75% Nearly 75% of all plaques on elbows and knees were clear or almost clear of redness and scaling by day 29**

¹Primary endpoint

²Secondary endpoint

**Important Safety Information**

SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. Systemic effects of topical corticosteroids may also manifest as Cushing’s syndrome, hyperglycemia or unmasking of latent diabetes mellitus, and glucosuria. These events are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high potency topical corticosteroids. Do not use if a trophic is present at the treatment site. Do not use with occlusive dressings. Avoid use on the face, scalp, axilla, groin or other intertriginous areas. Use of SERNIVO Spray is not recommended in pediatric patients as they are more susceptible to systemic toxicity. Allergic contact dermatitis may occur.

The most common adverse reactions (≥1%) were application site pruritus, burning and/or stinging, pain, and atrophy. Local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use, or use of higher potency corticosteroids. These are not all the possible side effects of SERNIVO Spray.

Please see Full Prescribing Information at SERNIVO.com and brief summary of prescribing information on adjacent page.

**Indication and Usage**

SERNIVO Spray is indicated for the treatment of mild-to-moderate plaque psoriasis in patients 18 years of age or older.

To report SUSPECTED SIDE EFFECTS, call Promius Pharma at 1-888-966-8766 or contact the FDA at 1-800-FDA-1088.

**References**

Minimize the unwanted risks from endocrine effects by mitigating the risk factors favoring increased systemic bioavailability and by using the product as recommended [see Dosage and Administration].

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of SERNIVO Spray is not recommended in pediatric patients [see Use in Specific Populations].

Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Corrobore a such an observation with appropriate diagnostic patch testing. If irritation develops, discontinue the topical corticosteroid and institute appropriate therapy.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In two randomized, multicenter, prospective vehicle-controlled clinical trials, subjects with moderate plaque psoriasis of the body applied SERNIVO Spray or vehicle spray twice daily for 4 weeks. A total of 352 subjects applied SERNIVO Spray and 180 subjects applied vehicle spray.

Adverse reactions that occurred in at least 1% of subjects treated with SERNIVO Spray for up to 28 days are presented in Table 1.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects Treated with SERNIVO Spray for up to Four Weeks

<table>
<thead>
<tr>
<th>Reaction</th>
<th>SERNIVO Spray b.i.d. (N=352)</th>
<th>Vehicle Spray b.i.d. (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pruritus</td>
<td>6.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Application site burning and/or stinging</td>
<td>4.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Application site pain</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Application site atrophy</td>
<td>1.1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Less common adverse reactions (with occurrence lower than 1% but higher than 0.1%) in subjects treated with SERNIVO spray were application site reactions including telangiectasia, dermatitis, discoloration, folliculitis and skin rash, in addition to dysgeusia and hyperglycemia. These adverse reactions were not observed in subjects treated with vehicle.

Postmarketing Experience
Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
“One way to try to work around such frivolous on-line statements is to have patients sign a waiver.”

Patient’s social posts ruined my reputation

by DAVID J. GOLDBERG, M.D., J.D.

Dr. Goldberg is director of Skin Laser and Surgery Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mt. Sinai; and, adjunct professor of law, Fordham Law School in New York City.

Dr. Derm has been in practice for three decades. He works hard, does no advertising, and does not even have a Facebook page. He is aware of peers who spend an extensive amount on marketing and social media; however he has had no interest. One day he finds out that a disgruntled patient has slandered his reputation on social media. In fact, he has been slandered on Facebook, Instagram, Yelp and Google.

This patient not only accused him of poor medical practice, but also videotaped his staff drinking beer in their nurse’s lounge. Even worse, the video has gone “viral” and has been seen by thousands. Dr. Derm is concerned this malicious act may ruin his career. The internet and social media are nothing more than a curse to Dr. Derm. Is there anything he can do?

Because of privacy laws, unfortunately, a physician has little recourse when an anonymous patient places a scathing review on a website. The reality is that even physician review sites are as likely to misinform as they are to inform. If a patient complains on-line that his surgical excision opened only two days after dermatologic surgery, there is no way for anybody to know whether the patient has performed strenuous exercise. Reviewers of these sites are generally not patients. There are known instances of dentists being accused on-line, by their competitors, of being child molesters. Similarly laudatory on-line comments can be written by the physician himself.

One way to try to work around such frivolous on-line statements is to have patients sign a waiver that has them promise that, in the case they are not happy with their care, they will not post on-line comments to that effect.

The way such contracts are enforceable is as follows: In general, websites acting as platforms for outside commentary are not liable for defamation suits. They are, according to North Carolina neurosurgeon-attorney Jeffrey Segal, subject to copyright laws. Waivers can be written to assign copyright to the treating physician. If the treating physician asks the patient to sign such a “copyright” waiver, the physician can claim ownership of any anonymous review of the practice and demand that such an on-line review then be removed.

There are now examples of website posts removing such deleterious copyrighted comments. Needless to say, not all patients will agree to sign such a waiver. Some may feel such waivers are simply “gag orders”. The reality is that disgruntled patients are free to speak with family, friends, other physicians, lawyers, hospital peer review committees, or credentialing committees. There are a wide range of appropriate and inappropriate places where patients can express their views.

Barring anonymous sites would be ideal. However, barring anonymous sites is unlikely to happen. At the very least it would be ideal if internet sites could verify that the “reviewer” is, in fact, a patient of the physician he or she is criticizing (or praising). Even more, to prevent the extreme opinion – positive and/or negative—from skewing impressions, websites should hold off from posting such reviews until they have at least 10 or more representative views. In an ideal situation reviews should focus on those aspects in which a patient would be expected to be knowledgeable. These would include issues such as waiting time, appropriate parking, or being treated rudely by the physician and/or staff. Commenting on physician technique or results is an entirely different issue.

Without any signed waiver in place, Dr. Derm is in no position to stop his patient from posting the negative on-line comments.
Q. What can be done for dandruff and seborrheic dermatitis from a cosmetic standpoint?

Oral and topical antifungals, along with topical corticosteroids, are the mainstay of prescription treatment for seborrheic dermatitis. However, once the severe scaling and itching has been controlled and the condition downgraded to dandruff, there still remains the need to prevent recurrence and control scaling. OTC products can be used for these purposes.

One way to prevent the recurrence of scalp dryness is to rub a normal hair instant conditioner into the scalp after shampooing, followed by rinsing. Conditioners can function as scalp moisturizers without leaving the scalp greasy, since they are rinsed minutes after application.

There are also many excellent anti-dandruff shampoos that are considered OTC drugs, but each shampoo can only contain one active agent. Thus, shampoos should be selected and rotated based on the needs of the patient. If the patient has adherent scalp scale, a salicylic acid shampoo is an excellent choice followed by an OTC salicylic acid scalp solution applied every evening to affected areas prior to bedtime.

If erythema and itching are primary, a tar shampoo is best to utilize for the anti-inflammatory effects, followed by an OTC hydrocortisone solution applied to the affected areas morning and evening as needed.

If prevention is the main goal, an antifungal shampoo that contains zinc pyrithione or selenium sulfide is best. Of these ingredients, the newer microfine zinc pyrithione products are the best, because the maximum allowed concentration of zinc pyrithione can be more evenly spread over the entire scalp. Thus, OTC dandruff products can augment prescription therapy in the healing and maintenance phase of seborrheic dermatitis.

Q. How can oily hair be controlled?

Oily hair is a common patient complaint, especially among adolescent females and males who may also present for acne treatment. It is important to remember that the hair does not make oil, but it does wick oil from the scalp down the hair shaft. If the hair is straight, the oil wicks rapidly from the scalp down the hair shaft. If the hair is tightly curled or kinky, the oil wicks more slowly. Oily hair is an indication of an oily scalp and requires scalp oil removal through frequent shampooing with a high detergent shampoo for oily hair. Preferably, no instant conditioner should be applied to the hair ends and immediately rinsed.

Another way to control scalp oil is to use one of the newly rediscovered dry shampoos. Dry hair shampoo was very popular in the 1950s, but has enjoyed renewed popularity. Dry shampoo is a powder that is dusted or sprayed onto the parted hair and scalp to absorb the oil, followed by combing or brushing to remove the excess powder. While dry hair shampoo does not replace wet shampooing, it can be used in the afternoon or evening to control an oily shine during the day.

Q. Are there any complications associated with the newly popular eyebrow threading?

Threading is a method of hair removal popular in the Middle East. It does not require tweezers or other equipment. Basically, two sewing threads are twisted back and forth and pulled between the two hands trapping the hairs and yanking them out of the skin. Stand-alone threading salons or hair salons with threading stations are appearing in the United States.

There is no difference between hair plucking or threading, tweezing, or waxing. All three methods yank the hair out of the follicle. There are no major complications with eyebrow threading, however, complications may occur. Excessively traumatic eyebrow hair removal may damage the follicle permanently destroying hair growth. Traumatic removal may also cause inflammatory folliculitis and possibly bacterial infection. Eyebrow threading is safe as long as the removal is done gently.
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Photos provided by Dr. Michael H. Gold, M.D., FAAD

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Topical for molluscum contagiosum performs well in phase 3 trials

VERRICA PHARMACEUTICALS announced in January that its novel therapeutic, VP-102, recently completed phase three CAMP-1 and CAMP-2 pivotal trials, demonstrating statistically significant improvements in patients with molluscum contagiosum, a chronic virus marked by pearl-like bumps on the skin primarily in children.

Currently, there are no FDA-approved treatments for the condition, but Verica has been sponsoring clinical trials for VP-102, its own novel topical solution consisting of 0.7% cantharidin. In each trial, VP-102 exhibited a clinically and statistically significant proportion of subjects demonstrating complete clearance of all treatable molluscum lesions versus placebo. VP-102 was well-tolerated in both trials, with no serious adverse events reported in VP-102 treated subjects, the company announced in a statement.

“We believe the efficacy and safety profiles of VP-102 observed in these two trials provide a strong foundation for our U.S. NDA which we intend to submit in the second half of this year,” said Ted White, Verica’s president and chief executive officer.

CAMP-1 and 2 are two randomized, double-blind, multicenter, placebo-controlled trials conducted at 31 centers in the United States. In total, the studies included patients two years old or older. The patients were treated once every 21 days for up to four applications for 12 weeks.

In CAMP-1, 46% of patients treated with VP-102 achieved complete clearance of all treatable molluscum lesions at day 84 versus 18% of placebo groups. In CAMP-2, 54% of treated patients achieve complete clearance as compared to 13% in the placebo group. And, also by the end of the trial, treated patients achieved a 69% and 83% mean reduction, respectively, in the number of molluscum lesions as compared to 20% and 19% for subjects on placebo.

Molluscum contagiosum affects six million people in the United States.

Clinical trials funding secured for antibacterial-resistant P. acnes treatment

VYOME THERAPEUTICS INC., announced in January that it secured $22 million in financing to, in part, support the development of its lead molecule, VB 1953, through phase two clinical trials for moderate to severe acne.

The closing of Vyome’s Series D comes at a transformational time for the company, as we prepare to initiate a phase 2b clinical trial with our lead candidate, VB 1953, and as we establish the center of operations and headquarters in the United States through a corporate restructuring exercise,” said Venkateswarlu Neelabhotla (Venkat), chief executive officer of Vyome Therapeutics. “We see this investment as validation of Vyome’s innovative approach to efficient specialty pharmaceutical development and the ability of the company’s scientific platform to help solve the problem of microbial resistance in dermatology.”

VB 1953 is a topical bactericidal antibiotic candidate with a novel mechanism of action that is designed to reduce inflammation. It is designed to treat antibiotic resistant P. acnes strains in which a phase 2b clinical trial is planned. In preclinical studies, VB 1953 was shown to be active against clindamycin-resistant P. acnes bacteria. It was shown to have a low emergence of resistance and to reduce inflammation.

VB 1953 is delivered with a microtechnology gel system that ensures the drug is retained at the site of infection and minimizes systemic exposure.

Non-melanoma skin cancer trial proceeds

SIRNAOMICS, INC., announced in December that it received FDA approval to proceed with phase two clinical trials for STP705, an siRNA (small interfering RNA) therapeutic for in situ Squamous Cell Carcinoma Nonmelanoma Skin Cancer (NMSC). Trials are expected to start in the first quarter of 2019.

STP705 works by inhibiting the expression of TGF-β1 and COX-2, enzymes that contribute to epithelial cell proliferation and the regulation, development and progression of NMSC.

“FDA clearance to proceed with the NMSC trial represents an important step forward in demonstrating the broader clinical utility of our siRNA platform,” said Sirnaomics’ founder and CEO Patrick Y. Lu, Ph.D. “Building on our technology’s potential against fibrotic disease, the drug target selection and tumor targeting delivery capabilities of our platform will help demonstrate the broader therapeutic potential of STP705 as a therapeutic candidate against cancer.”

The phase two trial will be led by Brian Berman, M.D., Ph.D., of the University of Miami Miller School of Medicine. “There is a real clinical need for non-invasive, targeted therapy for in situ squamous cell carcinoma,” Dr. Berman said in a news release.

Sirnaomics specializes in the discovery and development of RNAi therapeutics against cancer and fibrotic diseases.
VERSATILE. POWERFUL. ELEGANT.

THE NO-COMPROMISE TRIAMCINOLONE

TRIANEX® is the #1 prescribed branded topical triamcinolone.1

- Widespread use
- Nongreasy feel
- Day/night use
- No preservatives
- No age restrictions*
- Large 430g jar

*Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.

IMPORTANT SAFETY INFORMATION

The most common adverse events with TRIANEX Ointment include burning, itching, irritation, dryness, and folliculitis. TRIANEX Ointment is contraindicated in patients who are hypersensitive to any of the ingredients of this product. As with all topical corticosteroids, systemic absorption can produce reversible HPA-axis suppression.

INDICATION

TRIANEX 0.05% (Triamcinolone Acetonide Ointment, USP) is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

To report SUSPECTED SIDE EFFECTS, call Promius Pharma at 1-888-966-8766 or contact the FDA at 1-800-FDA-1088.

Please see Full Prescribing Information on adjacent page.

Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other skin conditions that increase skin permeability may enhance percutaneous absorption of topical corticosteroids. The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Some of the topical corticosteroids are metabolized by the liver and undergo further metabolism in the plasma. The biological activity of some of the topical corticosteroids is increased after metabolization in the liver. Therefore, topically applied corticosteroids may produce systemic effects in some patients.

INDICATIONS AND USAGE
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence:

Burning, Itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions,
Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin,
Infective dermatitis, Contact dermatitis, Irritant dermatitis, Paresthesia, Allergic contact dermatitis.

CLINICAL PHARMACOLOGY
Topical corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on nursing infants. Although teratogenicity has been observed in some laboratory animals, there are no adequate and well-controlled studies in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Pediatric Use
Topical corticosteroids are generally safe and well tolerated when used as directed. Their potential benefit should be considered against the possibility of growth suppression in children. Therefore, topical corticosteroids should be used in children only if the potential benefit justifies the potential risk to the child. Pediatric patients may demonstrate greater susceptibility to topical corticosteroid induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

CONTRAINDICATIONS
Triamcinolone Acetonide Ointment, USP is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and increased interstitial cell hyperplasia in some patients.

The following laboratory tests may be helpful in the diagnosis of HPA axis suppression: plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelle, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence: Burning, itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions, Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin, Secondary infection, Skin atrophy, Striae and Miliaria

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION
Any thin film to the affected area two to four times a day.

 Occlusive Dressing Technique
Occlusive dressings may be used for the management of peoriase or other recalcitrant conditions. Apply a thin film of ointment to the lesion, cover with a pliable nonporous film, and seal the edges. If needed, additional moisture may be provided by covering the lesion with a dampened clean cotton cloth before the nonporous film is applied or by briefly wetting the affected area with water immediately prior to applying the medication.

The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply Triamcinolone Acetonide Ointment under an occlusive dressing in the evening and to remove the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional ointment should be applied, without occlusion, during the day. Reaplication is essential at each dressing change. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

How Supplied
Triamcinolone Acetonide Ointment, USP is supplied in 430 g jars (NDC 67857-806-19).

Keep this and all drugs out of the reach of children.

You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Promius Pharma, LLC at 1-888-966-8766.

Keep this and all drugs out of the reach of children.

<Rx Only>
For external use only. Not for ophthalmic use.

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007850 Revised 0317
Psoriasis physician survey highlights need for effective therapies

A SURVEY OF 75 DERMATOLOGISTS who treat patients with moderate to severe psoriasis shows that among the greatest of unmet patient needs includes, in this order, the lack of safe and effective oral therapies, affordable treatments covered by insurance, treatment that is effective in maintaining long-term remission and lastly, topical treatments that work.

The survey, which was conducted between Nov. 21-26, was developed by InCrowd, a market intelligence firm specializing in healthcare.

This group of physicians reported treating an average of 79 patients with moderate to severe psoriasis over the course of three months; and, they described great interest in the development of new therapeutics, including IL-17/23/31 agents, JAK inhibitors and TYK2 inhibitors.

Of biologic and other non-biologic therapies doctors prescribe, these include: corticosteroids (58%); biologics (48%); generalized OTC products (22%); phototherapy (13%); PDE4 inhibitors (13%); topical or oral retinoids (11%); and, antibiotics (4%).

And, finally, in terms of treatment choice, Humira and Stelara were the most popular as shown in the graph on the right.

Q3 When thinking about treating your moderate to severe psoriasis patients, what is your most preferred treatment or drug for each of the lines of therapy below? (n=75)

Most Preferred Psoriasis Treatments By Lines of Therapy (open end feedback)

New fungal medication for the U.S. market

THE FOOD AND DRUG ADMINISTRATION (FDA) approved in December a new drug application for Tolsura (SUBA-itraconazole), a new formulation of itraconazole for the treatment of systemic fungal infections in adults.

Tolsura, which will be sold as 65 mg capsules, is indicated for the treatment of blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis) and aspergillosis (pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy). These infections occur in vulnerable or immunocompromised patients, such as patients with a history of cancer, transplants (solid organ or bone marrow), HIV/AIDS, or chronic rheumatic disorders. They are often associated with high mortality rates or long-term health issues, according to Mayne Pharma Group Limited, which issued a statement about the approval.

Mayne Pharma expects to launch the product in the U.S. by the end of first quarter 2019. It is one of more than 60 products the company markets in the United States, including Fabior (tazarotene) foam, Sorilux (calcipotriene) foam and Doryx MPC (doxycycline) delayed-release tablets. They recently acquired Lexelle (halobetasol) foam for plaque psoriasis which is also expected to be launched by end of the first quarter 2019.
It’s been rewarding to watch dermatology develop treatments for things we once couldn’t help. And, there’s more promising areas like that on the way.

Brett Coldiron, M.D., President, Ohio Dermatological Foundation and clinical associate professor at the University of Cincinnati
While as many as 1 out of every 5 healthy children contract molluscum contagiosum, this disease and the patients it affects receive very little attention.¹ Quality of life can be negatively affected by a molluscum infection.² Children with the disease may become stigmatized and experience teasing, embarrassment, and social isolation. Up to 82% of parents and caregivers express moderate to great concern about molluscum.³ Lesions may be mostly asymptomatic, but reports indicate that patients do complain about itching, burning, and tenderness.³

Although lesions can resolve within 6 to 9 months, patients typically have the infection for 13 months, and some infections can persist for 2 years or more.²,³ Treatment at the time of diagnosis provides the best chance of decreasing the number of lesions and spread of the disease.³

No current FDA-approved treatment option addresses the problem of successfully treating molluscum.

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References
Healthcare disparities exist in all fields of medicine, including dermatology. Despite movements to educate the general public, many myths related to dermatology still exist, such as the belief that those with darker skin tones do not need to protect their skin because they have a minimal risk of developing skin cancer. While it is true that increased amounts of melanin and the mechanisms related to melanosomes in people with skin of color do provide a significant level of photoprotection, they are still at risk for all the same conditions that affect lighter skin types; though, these conditions may present differently and have poorer outcomes.

The purpose of this brief review is to focus on some differences in epidemiology, presentation, access, and outcomes in different skin types for five dermatologic conditions: atopic dermatitis, melanoma, hidradenitis suppurativa, melasma, and vitiligo.

**Skin and disparity issues that affect patients with skin of color**

*by MARIA L. ESPINOSA, B.S., & PETER A. LIO, M.D.*

Maria L. Espinosa is a medical student at The University of Chicago Pritzker School of Medicine. Peter A. Lio, MD is a clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine and a partner at Medical Dermatology Associates of Chicago.

Atopic dermatitis (AD) is an increasingly common condition estimated to affect over 30 million children and adults in America of all colors, albeit with significant differences in prevalence, response to treatment, and molecular biology. In population studies, AD has been found to be more prevalent in African American and Asian/Pacific Islander individuals than Caucasians. This may be explained by increased inflammation due to higher affinity IgE receptors and decreased innate immune markers including Th1 and Th17 found in African Americans when compared to European Americans with the condition. As Sanyal and colleagues discuss in their article, differences on the molecular level may begin to explain why African Americans don’t respond to treatment exactly like other groups, and tend to require higher levels of corticosteroids, have a higher risk for hypopigmentation, and are more likely to need higher doses of cyclosporine A and ultraviolet B light. Similar studies examining Asians and Pacific Islander populations found that their immune system has a stronger Th17/Th22 response compared to Caucasians, leading to increased inflammation and more pronounced presentation of AD, especially since it tends to present as a mix of AD and psoriasis in this population. Notably, the markers Th2, Th22, and IgE are all correlated with increased AD severity, and these are markers that are more common in African American and Asian populations.

In terms of presentation, African Americans have increased risk for post-inflammatory dyspigmentation, plaques on extensor surfaces instead of traditional flexor surfaces and have scattered distinct plaques; while Asian patients more likely to have scaling and lichenification than Caucasians. Another layer of complexity is added when examining the disparities between the healthcare access in populations affected by AD. For example, non-Hispanic blacks had 33% lower odds of keeping follow-up appointments for their AD, and those that did access medical care had more ambulatory visits and filled more prescriptions than non-Hispanic whites. These molecular differences amongst populations affected by AD make it crucial to continue increasing diversity in clinical trials in order to obtain personalized, evidence based treatment recommendations for patients with each skin type.

Melanoma: The disparities related to melanoma are quite striking. Although 95% of cases are diagnosed in people with white or light skin, the remaining 5% of cases in African Americans and Hispanics have poorer prognosis due to diagnosis at more advanced stages and the subtype of melanoma. Multiple studies have found that the 5-year survival rate in African Americans and Hispanics is much lower than that of Caucasians, 72% to 81% versus 90%. People of color diagnosed with melanoma tend to have the acral lentiginous subtype, which is more invasive. Focusing on Hispanic populations, it has...
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DMARD, disease-modifying antirheumatic drug.

Please see accompanying Brief Summary of Full Prescribing Information.


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For patients with moderate to severe plaque psoriasis

RESULTS — the way — THEY WANT THEM

Otezla® has a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring—making it a treatment experience patients can respond to

Otezla® (apremilast) significantly increased PASI-75 response (n = 562) at week 16 (primary endpoint) vs placebo (n = 282) (33% vs 5%; P < 0.0001) in ESTEEM 1,2

ESTEEM® Study Design
- Evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration
- Selected inclusion criteria: age ≥18 years, BSA ≥10%, sPGA ≥3, PASI ≥12, candidates for phototherapy or systemic therapy

INDICATIONS
Otezla® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla® is indicated for the treatment of adult patients with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION
Contraindications
- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions
- Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on
Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

- Weight Decrease: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients taking placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla.

- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

**Adverse Reactions**

- Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4).

**Use in Specific Populations**

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman.

- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information.

*Following a 5-day titration, the recommended maintenance dosage is 30 mg twice daily.

† To receive a free bridge supply of Otezla, patients must have an on-label diagnosis and be denied or waiting for coverage. Patients in Massachusetts are not eligible to receive bridge.

‡ Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call 1-844-4OTEZLA to discuss other financial assistance opportunities.

BSA, body surface area; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI, Psoriasis Area and Severity Index; SPGA, static Physician Global Assessment.


**Please turn the page for Brief Summary of Full Prescribing Information.**

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OTEZLA® (apremilast) tablets, for oral use

The following is a Brief Summary; refer to Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
OTEZLA® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

CONTRAINDICATIONS
OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS
Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reductions in patients with severe diarrhea, nausea, or vomiting.

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of patients treated with OTEZLA experienced discontinuation due to depression compared to none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of patients while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of patients treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of 2-10% of body weight occurred in 2% (16/784) of patients treated with OTEZLA 30 mg twice daily compared to 1% (3/382) patients treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS
Clinical Trials Experience in Psoriasis: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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. Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (5.6%), diarrhea (1.0%), and headache (0.8%). The proportion of patients with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for patients treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated patients.

Table 3: Adverse Reactions Reported in ≥2% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N=506)</th>
<th>OTEZLA 30 mg BID (N=920)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>32 (6)</td>
<td>160 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (7)</td>
<td>155 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (6)</td>
<td>84 (9)</td>
</tr>
<tr>
<td>Tension headache</td>
<td>21 (4)</td>
<td>75 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>11 (2)</td>
<td>39 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (2)</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (2)</td>
<td>29 (3)</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>5 (1)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (1)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (1)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (1)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>1 (0)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Tooth abscess</td>
<td>0 (0)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Falliculitis</td>
<td>0 (0)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>0 (0)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) patients following discontinuation of treatment with OTEZLA (apremilast).

DRUG INTERACTIONS
Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category C: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-317-8972. Nursing Mothers: It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman. Pediatric use: The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established. Geriatric use: Of the 1257 patients who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis patients were 65 years of age and older, including 9 patients who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly patients ≥65 years of age and younger adult patients <65 years of age in the clinical trials. Renal impairment: Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

Hepatic Impairment: Apremilast pharmacokinetics were characterized in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

OVERDOSAGE
In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Based on APRPI.006 OTZ_PsO_HCP_BSv.006 06_2017
Skin condition disparities compared

Atopic Dermatitis

**PREVALENCE**
- More prevalent in African American and Asian/Pacific Islanders individuals than Caucasians.

**DISPARITY**
- Non-Hispanic blacks had 33% lower odds of keeping follow-up appointments for their AD, and those that did access medical care had more ambulatory visits and filled more prescriptions than non-Hispanic whites.

Melanoma

**PREVALENCE**
- 95% of cases are diagnosed in people with white or light skin; the remaining 5% of cases in African Americans and Hispanics.

**DISPARITY**
- People of color tend to be diagnosed with the more invasive subtype of acral lentiginous melanoma;
- Hispanic population 20% less likely than non-Hispanics to perform skin self-examination;
- 5-year survival rate in African Americans (72%) and Hispanics (81%) is much lower than that of Caucasians (90%).

Hidradenitis Suppurativa

**PREVALENCE**
- Affects up to 4% of the American population;
- Affects about 1% of the population, incidence does not vary by skin color, and it affects men and women equally.

**DISPARITY**
- Found to be associated with lower socioeconomic status;
- African American women have been found to be more likely to fail medical treatment and undergo surgery for this disease.

Melasma

**PREVALENCE**
- Affects up to 4% of the American population;
- National and worldwide prevalence is unknown;
- More common in populations of Hispanic, African, and Asian/Pacific Islander descent;
- Pigmentation disorders overall are within the top 5 most common dermatologic concerns.

**DISPARITY**
- Populations closer to the equator, or more tropical conditions tend to have more risk factors for worsening melasma.

Vitiligo

**PREVALENCE**
- Affects about 1% of the population,
- More likely to fail conservative treatments and are more likely to need phototherapy, which can be more expensive and time consuming;
- Patients with darker skin types (Middle Eastern, Caribbean and Indian heritage) perceive greater burden compared to lighter-skinned individuals;
- African Americans experience loss of racial identity.

**DISPARITY**
- The overall stress associated with vitiligo was the same across ethnic groups in more recent works.

DISPARITIES IN CARE

been found that they are about 20% less likely than non-Hispanics to perform a skin self-examination. Alarming, the prevalence of physician skin exams varied by patient language abilities. One study surveyed 4,766 individuals who identified as Hispanic, and found that patients who mostly or only spoke Spanish were almost three times less likely to report ever having had a physician skin examination compared to Hispanic patients who mostly or only spoke English. This suggests that increasing the diversity of dermatologists may increase skin cancer detection by making patients feel more comfortable communicating with a provider that speaks their language and knows their cultural practices.

**HIDRADENITIS SUPPURATIVA**

Hidradenitis Suppurativa (HS) is a chronic inflammatory condition that affects up to 4% of the American population, and in several studies in the United States has been found to be more common in African American and Hispanic female patients. This may be due to these two populations being more likely to be obese, have metabolic syndrome, and smoke cigarettes, all of which are risk factors for the development of HS. In a Dutch population, this disease was found to be associated with lower socioeconomic status. Low socioeconomic status makes it difficult for families to buy fresh produce, and their neighborhoods may preclude them from exercising outside for safety reasons, thereby contributing to obesity and metabolic syndrome and ultimately dermatologic conditions such as acanthosis nigricans and HS.

Anatomic and genetic differences also play a role in the differences in HS across ethnic groups. A study in the early 1900s concluded that people of African heritage had three times the amount of apocrine glands as compared to Caucasians, a finding that is striking and prompts further investigation. Few studies have looked at the genetic differences in patients affected by HS, and no trials to date have examined the efficacy of adalimumab, the gold standard FDA approved medication, across ethnic groups. This is important because African American women have been found to be more likely to fail medical treatment and undergo surgery for this disease. Patients that lack access to healthy foods and exercise are at increased risk for metabolic problems, and, ultimately, skin manifestations. It is the role of dermatologists...
There are important differences affecting people of color that need to be addressed and explored.

Maria L. Espinosa, medical student at The University of Chicago Pritzker School of Medicine and Peter A. Lio, M.D., Northwestern University Feinberg School of Medicine

MELASMA
Melasma is a common condition of hyperpigmentation primarily occurring on the face and other sun exposed areas. The national and worldwide prevalence is unknown, however many studies have found that it is more common in populations of Hispanic, African, and Asian/Pacific Islander descent, and pigmentation disorders overall are within the top 5 most common dermatologic concerns. Melasma is influenced by hormones, and is more likely to arise or worsen in pregnancy and in women taking oral contraceptives. Beyond encouraging all patients to use appropriate sun protection, treatment response varies by a patient’s skin type. Patients with darker skin are at higher risk for post-inflammatory hyperpigmentation after laser therapy, and further dyspigmentation and keloid formation following deep peel treatments. In addition to patients’ concern about appearance, melasma greatly affects every day life, including social interactions, health and financial concerns. Patients with melasma have higher rates of anxiety and depression, and are more likely to take antidepressants than those without the condition.

Finally, the most prominent risk factor for melasma onset and exacerbation is sun exposure. One small cohort study looking at Puerto Rican women found that in all cases, their mandibular melasma was exacerbated by sun exposure and lead to hyperpigmentation on histology. This finding suggests that populations closer to the equator, or more tropical conditions tend to have more risk factors for worsening melasma. Mahmoud and colleagues tested this concept and found that both visible light (400-700nm) and long-wavelength UVA1 (340-400nm) caused more prominent pigmentation in volunteers with darker skin (Fitzpatrick IV-VI), than those with skin type II, suggesting that even broader-spectrum sunscreens should be recommended, including those with iron oxide as a tint to help block visible light. Sun protection, thus, seems every bit as important for patients with skin of color: in addition to increasing the risk of skin cancer, sun exposure also plays a critical role in pigmentary disorders.

UNITED COLORS OF DERMATOLOGY
There are important differences affecting people of color that need to be addressed and explored. Ideally, dermatologists will unite around their patients by continuing public education on skin exams and skin protection in various languages, and working with primary care colleagues to enhance screening and referrals. Increasing diversity among practicing dermatologists may also help to combat these disparities. While patients may feel more comfortable and increasing diversity in medicine will likely help, until that time, it is important to be aware of these disparities and important differences.

Any dermatologist can become more knowledgeable about these issues by joining the Skin of Color society, whose mission to educate both providers and patients on issues related to the wellbeing of skin of color. There is also a need to increase diversity of enrollment in research trials, and make them more representative of the populations most affected by each condition in order to ultimately have evidence-based treatment recommendations for each skin type. In the meantime, we hope to continue to explore these issues, and strive to improve outcomes for all.
ALL ABOARD ONEXTON GEL

Efficacy and tolerability matter when it comes to treating acne. In the pivotal trial, ONEXTON GEL was shown to treat both inflammatory and noninflammatory acne, and no patients discontinued due to an adverse event.1,2

TOLERABILITY > EFFICACY

INDICATION
ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

IMPORTANT SAFETY INFORMATION
• ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation, or lincomycin.
• ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
• Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
• Orale and parenterally administered clindamycin has been associated with severe colitis, which may result in death.
• Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact a physician immediately.
• The most common local adverse reactions experienced by patients in clinical trials were mild and moderate erythema, scaling, itching, burning and stinging.

• ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
• ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.
• Patients should be advised to avoid contact with the eyes or mucous membranes.
• Patients should minimize exposure to natural and artificial sunlight (tanning beds or UVA/UVB treatment) while using ONEXTON Gel. To minimize exposure to sunlight, protective clothing should be worn and a sunscreen with SPF 15 rating or higher should be used.

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

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


LEARN MORE AT ONEXTON.COM

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Contraindications

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If diarrhea occurs, ONEXTON Gel should be discontinued. Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antibiotic-associated colitis such as pseudomembranous colitis may develop and may be associated with the passage of blood and mucus. Stool cultures forClostridium difficile and stool assay forC difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see Nonclinical Toxicology].

Adverse Reactions

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label: colitis [see Warnings and Precautions].

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice. These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel:

- Burning sensation
- Contact dermatitis
- Pruritus
- Rash

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel and may not reflect the rates observed in clinical practice. Because clinical trials are conducted under widely varying conditions, adverse reaction rates reported from clinical trials of another drug may not reflect the rates observed in clinical practice.

Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetic acid at doses of 5 and 10 mg administered topically twice per week for 2 weeks induced skin tumors in transgenic Tg AC mice. The clinical significance of this is unknown. Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 950, 2700, and 15000 mg/kg/day, and 30 times amount of clindamycin and 2, 4, 7, 2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m2 respectively did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/ day caused a dose-dependent increase in the incidence of keratinocarcinoma at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900, and 3000 mg/kg/day, and 12 times amount of clindamycin and 1, 6, 4, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m2 respectively for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, 40 weeks of treatment followed by 12 weeks of observation, the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation. Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in S. typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 2000 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m2) revealed no effects on fertility or mating ability.

Hypersensitivity

Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

Drug Interactions

Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritation or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

Patient Counseling Information

See FDA-approved patient labeling (Patient Information).

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By: Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
U.S. Patent 8,288,434
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ONX.00811.AEA.18
REFERENCES


TRENDS TO WATCH INCLUDE TECHNOLOGY, THERAPEUTIC AND WORKFLOW ADVANCES FROM PAGE 18

NEW THERAPEUTICS
Alongside technology advances, the future also holds new medications and therapies, said Seema Desai, M.D., president of the Skin of Color Society and president and medical director for Innovative Dermatology, PA, in Texas.

“There are a couple of things in development that will be used for diseases we haven’t had FDA-approved treatments for,” she said. “It’s really new and exciting that these things are being done.”

JAK inhibitors: This class of drug, including tofacitinib (Xeljanz, Pfizer) and ruxolitinib (Jakafi, Incyte Corp.), is already used to treat rheumatoid arthritis, Dr. Desai said, but current research is investigating its utility for treating vitiligo, alopecia areata, and psoriasis.Phase I trials are also underway for additional JAK inhibitors.

Gene & stem cell therapy: The National Institutes of Health is also beginning to fund research into genetic and rare skin conditions with no existing treatments, he said.

WORKFLOW
The coming years are also likely to change how dermatologists manage their daily activities.

Physician extenders: Physician assistants and nurse practitioners will likely provide more dermatology care, Dr. Coldiron said, as aging dermatologists retire and patient volumes continue to rise. He cautioned dermatologists to closely supervise these extenders and to have them provide care during follow-up visits for existing patients, never for an initial appointment.

Ultimately, he said, dermatology can look forward to many positive developments.

“It’s the most attractive specialty in all of medicine,” Dr. Coldiron said. “It’s been rewarding to watch dermatology develop treatments for things we once couldn’t help. And, there’s more promising areas like that on the way.”

DISPARITIES IN CARE FROM PAGE 26
Options for foot dermatoses

Effective treatment can be provided at minimal patient expense

WHITNEY J. PALMER | Staff Correspondent

Dermatological conditions that lead to foot pain and discomfort do not necessarily require costly and time-consuming prescription management. Instead, according to a new study, over-the-counter treatments can be a viable option for patients.

Some type of foot-related condition affects as much as 30% of the general U.S. population. According to a review study published recently in American Family Physician, “Common Foot Problems: Over-the-Counter Treatments and Home Care,” patients can achieve some level of improvement and relief from plantar warts, corns and calluses, tinea pedis (Athlete’s foot), and onychomycosis (toenail fungus) without expensive medications.

The goal of the study, said Blair Becker, M.D., study author and primary care physician with Kaiser Permanente Washington Family Medicine Residency in Seattle, is to arm providers with a variety of treatment options patients can implement on their own with limited out-of-pocket expense or time spent in doctor’s appointments.

“We’re trying to give providers more tools for when they see conditions pop up that are more cost effective and also have some evidence behind them,” Becker said. “As physicians, we want to have confidence in recommending things that will actually help our patients.”

The study addresses several conditions commonly seen in both dermatology and primary care offices and outlines treatment options that have been tested in randomized, controlled trials.

“We want folks to be diagnosed correctly and to have guidance, so we’re not eliminating the physician from the situation,” he said. “But, it’s nice to be able to offer over-the-counter remedies because they’re so cost-effective.”

PLANTAR WARTS
Linked to the human papillomavirus, plantar warts occur most frequently in children. Approximately 20% of children ages 4 to 12 will experience a viral plantar wart. Roughly two-thirds of lesions will likely clear up on their own within two years of appearance, but how quickly it resolves depends on which virus strain is involved.

Existing evidence points to several effective, inexpensive over-the-counter therapies, he said. Based on the results of one randomized, controlled trial, 90% of patients reach a cure using a variety of cryotherapy agents, including liquid nitrogen, dimethyl ether, and propane. Results were the same among patients who treated their warts in two-, three-, or four-week intervals.

In addition, salicylic acid and zinc oxide have also been shown to reduce the impact of plantar warts with similar efficacy to cryotherapy.

CORNs AND CALLUSES
Pressure and friction on the skin are responsible for corn and calluses. The most effective treatments for these hyperkeratotic conditions are ones that give the skin time to heal. Donut pads and metatarsal bars are commonly-used solutions that can redirect pressure away from a lesion, but existing evidence has revealed salicylic acid is also an effective over-the-counter tool in reducing their impact, Dr. Becker said. Applying salicylic acid softens them, and using salicylic acid plasters, over time, encourages the corn or callus to sluff away.

Tinea Pedis (Athlete’s Foot)
As one of the most common dermatologic foot conditions, tinea pedis can appear in as many as 50% to 80% of patients, increasing the need for a read-

Quick Takes
Foot discomfort does not necessarily require costly prescription management.

Patients can achieve relief from foot dermatoses with a variety of OTC options.

Review aims to identify multiple cost-effective solutions providers can offer patients.

30% percentage of general U.S. population that has some type of foot-related condition.
Too tool to diagnose nail fungus

Rising incidence makes more efficient ID of cause a priority

**As physicians, we want to have confidence in recommending things that will actually help our patients.”**

Blair Becker, M.D., Kaiser Permanente Washington Family Medicine Residency, Seattle

**Quick Takes**

Attenuated total reflectance Fourier transform infrared spectroscopy may be effective tool to improve diagnosis.

To test ATR-FTIR efficacy, researchers included 73 adults without suspected onychomycosis in an ex vivo model and 19 patients with possible onychomycosis in an in vivo model.

Researchers conducted four classification models, differentiating several factors, including dermatophytes species causing infection.

**For** the last several decades, global incidence rates of onychomycosis have risen, but there still is no method to quickly and accurately identify which organism causes infection.

As a chronic condition, onychomycosis lingers. Without treatment, it can spread and destroy the nail. According to a new study, attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) could be the fast, affordable, effective tool that improves diagnosis.

Based on the study published in the *British Journal of Dermatology,* the condition has been increasing in prevalence in relation to its most significant risk factors, including diabetes mellitus and occlusive footwear. This higher incidence makes more efficient identification of the causes behind onychomycosis a priority, particularly because the condition can present similarly to other onychopathies, such as nail psoriasis.

ATR-FTIR is an absorptive method that uses radiation beams to analyze and identify biological samples. Each fungal cell wall, mainly composed of glycoproteins and polysaccharides, is well-suited for this type of classification because each has a unique structure and biosynthesis. It can also recognize minor cell wall components that vary among fungi species.

This analysis surpasses current methods, including potassium hydroxide preparation, histopathological examination with periodic acid-Schiffstain, culture, and polymerase chain reaction (PCR) assays. These tactics are slower, more complex, lack sensitivity, provide false negatives, and they require trained personnel, the researchers reported.

By contrast, Dr. de Bruye said, infrared spectroscopy is fast, simple, non-destructive, and portable for in-field work. It also requires a minimal level of expertise to conduct, and it has the relatively low set-up cost of the one-time expense for the ATR-FTIR spectrometer.

To test ATR-FTIR efficacy, researchers created ex vivo and in vivo models. The ex vivo model included 158 distal fingernails and 159 toenails from 73 adults without suspected onychomycosis, and the in vivo model included distal toenails from 19 patients with possible onychomycosis. Investigators watched ex vivo samples for growth over two weeks and in vivo samples for four weeks. Ex vivo nails were examined in tact, and in vivo samples were powdered to ensure homogeneity because macroscopic changes, including nail thickening or irregular surfaces, can augment spectral noise.

With the ex vivo nails, researchers conducted four classification models, differentiating between uninfected and infected nails, various dermatophytes species causing infection, as well as nails infected with non-dermatophytes and yeasts. Using dendograms, they investigated whether ATR-FTIR could be a more accessible diagnostic option.

They analyzed the spectral differences of 32 fungal microorganisms, including 20 dermatophytes (1692-1606 and 1044-1004 cm⁻¹), 8 non-dermatophytes (973-937 cm⁻¹), and 4 yeasts (973-937 cm⁻¹). Using ex vivo nails, results showed prominent differences from 1200-900 cm⁻¹ with accurate classification rates of dermatophytes, non-dermatophytes, and yeast of 91%, 97.7%, and 98.6%, respectively.

From the 19 nails in the in vivo model, 12 samples were positive for infection. Seven were identified as *T. rubrum,* and two were identified as *Candida parapsilosis.* Investigators found distinct spectral differences in the 1043-950 cm⁻¹ region, as well as the 3000-2811 cm⁻¹, and the 1676-1553 cm⁻¹.

The ex vivo model revealed the carbohydrate region is the most efficient in pinpointing the discriminating features of a fungus and that FTIR spectroscopic examination of pol-
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*Based on available 510(k) summaries as of October 2017.

Foot dermatoses can be treated at minimal cost to patient FROM PAGE 30

However, patients have tried creative solutions, he said, to uncertain results. For example, many patients have employed Tea tree oil, topically-applied cough suppressants, confiserous resin, and sunflower oil with their toenail fungus. But, there is no clinical evidence to support the effectiveness of these therapies. In addition, there is no data to support treating nail infections with the over-the-counter antifungal creams used to treat tinea pedis.

In many cases, though, patients opt to forego onychomycosis treatment, despite the discomfort it presents, because of the side effects, he said. “Onychomycosis is prevalent and difficult to eradicate. And, in addition to being a cosmetic issue for a lot of people, it’s also uncomfortable as it gets in the nail, thickens it, and can change it’s shape,” Dr. Becker said. “Unfortunately, antifungal pills are the only ones with good evidence of being helpful, and they can be hard on the liver and require many months of treatment with regular liver monitoring and testing.”

Consequently, he said, after conversations with their doctor, many patients decide against taking the medication.

The ultimate assumption, Dr. Becker said, is most primary care and dermatology providers want to give patients evidence-based, accessible solutions that can effectively treat their foot conditions. “There are a lot of other treatments out there for these conditions. Our goal was to highlight solutions that people can use with direction from their primary care physician,” Dr. Becker said. “As primary care providers, we try to eliminate a patient’s expense and the hassle of their coming in to be seen as much as we can. We know their money and time are tight, and this is a way that we, as any type of provider, can help.”

Reference:

Foot dermatoses can be treated at minimal cost to patient FROM PAGE 30

ysaccharide content could be a reliable method for detecting and differentiating which organism prompts onychomycosis.

“These results show that FTIR spectroscopic examination of the polysaccharide content could be a reliable technique for the detection and differentiation of causative organisms of onychomycosis,” Dr. de Bruye said.

In vivo model results confirmed those findings.

In addition to identifying spectral differences, Dr. de Bruye said, ATR-FTIR offers several clinical benefits. There is current debate about whether to conduct confirmatory testing before launching treatment due to the cost and time-consuming nature of the testing. ATR-FTIR could significantly reduce delays in diagnosis and treatment, he said, because it does not require any reagents or extensive sample handling. The information gathered could also be used for providing a posteriori diagnostic analysis for other applications, including psoriasis and diabetes mellitus diagnoses. Different biochemical fingerprints of psoriatic and onychomycotic nails could further enhance diagnostic tools, as well.

The researchers did caution, however, that while false-negative or false-positive are unlikely, ATR-FTIR might also pick up spectral characteristics from contaminating bacteria, such as green nail syndrome. In those situations, a fungal culture might still be necessary for making a correct identification and determining a proper treatment plan.

Ultimately, Dr. de Bruye said, ATR-FTIR holds a great deal of promise for improving how dermatologists approach treating onychomycosis in patients. But, more work is required.

“Based on our findings, it can be stated that ATR-FTIR spectroscopy could be a promising technique for the diagnosis of onychomycosis,” he said. “However, large-scale investigations on clinical onychomycosis diagnostics are necessary to determine and validate its definite position compared to currently employed techniques.”

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Routine, according to Dr. Rosen. Topical steroids helped but didn’t clear her skin. And because the atopic dermatitis involved thin skinned areas of her face, neck and fossa, Dr. Rosen says long-term use of ultrapotent steroids like topical clobetasol or halobetasol was not an option. Mild or mid-potent steroids didn’t make much of an impact, and antihistamines didn’t help at all.

“So we embarked on the next level of therapy: methotrexate, which is sort of my fallback systemic drug. She didn’t tolerate methotrexate,” he says. In fact, the patient had more than a five-fold increase in her baseline liver function test.

“It’s somewhere between three and five times that you start worrying about actually causing liver damage,” he says. Next in line, Dr. Rosen tried cyclosporin, another go-to drug for moderate-to-severe adult atopic dermatitis. The patient had never been hypertensive but developed hypertension on cyclosporin, with significant systolic and diastolic elevations.

“We stopped the cyclosporin, re-challenged and she developed hypertension again. So, click that one off,” he says.

Dr. Rosen tried azathioprine (Imuran, Sebela Pharmaceuticals). She didn’t tolerate that drug, either. The patient experienced gastrointestinal side effects, including nausea, vomiting and diarrhea to the point of dehydration.

“Then, not because I think it’s the best drug but because I’m running out of options, I gave her mycophenolate mofetil (CellCept, Genentech) and that did nothing, even after allowing time for it to work,” he says.

She wasn’t a good candidate for phototherapy because of her fair skin and history with diagnoses of actinic keratosis, basal cell carcinoma and squamous cell carcinoma.

“While phototherapy might have been beneficial for her atopic dermatitis, it was really contraindicated because of her background of nonmelanoma skin cancer. You don’t want to do phototherapy on someone with a long history of skin cancer,” Dr. Rosen says.

The drug that finally worked after all the others failed was dupilumab, (Dupixent, Sanofi). The patient was able, with difficulty, to convince her insurance carrier to pay for the biologic—an IL 13 and IL 4 inhibitor that is approved by the U.S. Food and Drug Administration to treat atopic dermatitis.

The patient was able, with difficulty, to convince her insurance carrier to pay for the biologic—an IL 13 and IL 4 inhibitor that is approved by the U.S. Food and Drug Administration to treat atopic dermatitis.

A year into treatment with dupilumab, the patient remains mostly clear. The only side effect has been eye irritation, which hasn’t reached the level of conjunctivitis or blepharitis, according to Dr. Rosen.

Dermatologists might face hurdles getting insurers to approve expensive biologics like dupilumab, he says, but it’s worth jumping those hurdles.

THE TAKEAWAY LESSON

“Here’s the message (besides you’ve given me my life back): don’t wait. Go to the most efficacious agent that’s appropriate for patients as soon as it’s feasible,” Dr. Rosen says. “If there’s a patient objection to receiving a biologic drug, try and address it and skip ahead. I probably overdid trying different things. I think it’s reasonable to try an agent like methotrexate or cyclosporin and if that agent doesn’t work, plead your patient’s case to insurance carrier for a biologic.”

It’s an important lesson because dermatologists will have several such medicines from which to choose to treat atopic dermatitis in the coming years, according to Dr. Rosen.
Hemangioma distribution not random, study shows

BOB KRONEMYER | Staff Correspondent

The distribution of localized infantile hemangiomas of the face and scalp favor involvement of the midline face, scalp, and ocular axis, shows a retrospective review published in the journal Pediatric Dermatology.

“Although previous studies have indicated that localized hemangiomas may have a predilection for sites of fusion between embryologic subunits, including the frontonasal, maxillary, and mandibular prominences, our study did not confirm this. Instead, the hemangiomas occurred most commonly along the ocular axis, which includes the region running horizontally across the eyes and the vertical midline facial axis, with higher densities on the nasal tip and perioral region of the face,” wrote the authors who were led by Anita N. Haggstrom, M.D., of Indiana University. The study was published online August 31, 2018.

Dr. Haggstrom tells Dermatology Times that many clinicians who see large numbers of patients with infantile hemangiomas, have observed specific commonly affected sites.

“Previous studies had suggested a predilection of localized hemangiomas along the borders of facial developmental segments, and it was postulated that perhaps there were local areas of tissue hypoxia at these borders that stimulated hemangiomma growth,” Dr. Haggstrom said. “However, our study did not confirm these findings, which was somewhat surprising. The strong predilection for the midline for scalp hemangiomas was likewise unexpected.”

The study concluded that the regions corresponding to the boundaries between the embryonic facial segments, including the maxillary and mandibular metamers, were no more prevalent in the distribution of infantile hemangiomas.

The results also differ from a 2016 study in Pediatric Dermatology that evaluated the distribution of lip hemangiomas, in which upper lip infantile hemangiomas were much more common than lower lip.

“Our study demonstrated a lower lip predilection,” Dr. Haggstrom says. “Conversely, midline hemangiomas of the head and neck are not rare and, in fact, are a common presentation that should not prompt more extensive workup, which may be reassuring to primary caregivers.”

**THE STUDY**

Researchers evaluated 4,153 local face and scalp infantile hemangiomas from 10 pediatric dermatology healthcare centers. The hemangiomas were mapped with heat-map software using standardized facial templates displaying frontal and lateral views of the face and frontal, lateral, top, and posterior views of the scalp.

Seventy-one percent of the hemangiomas were mapped to a frontal facial template, of which 73.8% occurred along the midline axis or perpendicularly across the ocular axis in a cross-shaped area of predilection intersecting at the glabella.

Scalp hemangiomas showed a predilection for the midline with 50.5% (149 of 295) observed on the top of the scalp at the midline.

Localized hemangiomas did not indicate a preferential laterality.

**SIGNIFICANCE**

“The study shows novel areas of predilection for infantile hemangiomas, which may eventually help guide our understanding of hemangioma pathogenesis,” Dr. Haggstrom said.

From a developmental prospective, it is unclear why infantile hemangiomas are more frequent at some anatomic sites, despite evidence that infants with these tumors have an increased number of circulating endothelial progenitor cells.

The results of the current study beg more questions, Dr. Haggstrom said. “Why do these hemangiomas occur in these locations?” she says. "Are there tissue factors specific to these areas that lend just the right environment for hemangioma growth? Ultimately, we would like the study to contribute to our understanding of hemangioma development.”

Dr. Haggstrom and her associates are now looking more closely at other types of infantile hemangiomas and the patterns in which they occur.

“We are also trying to identify high-risk versus low-risk patterns to help guide physician management,” she said. 

**Reference**


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Combined therapy shows promise in mouse model

Combining the antibody IgG2a(TA99) with the recombinant TA99-mTNF fusion protein improves the effectiveness of the antibody against melanoma in mice, a study published in The Journal of Investigative Dermatology has shown.1

The murine TA99 antibody targets the cell membrane gp75 antigen which is selectively expressed in melanocytes and in melanoma cells, but is undetectable in all other normal tissues and, therefore, represents an ideal target for antibody-based pharmaceutical applications.

“These findings may open new clinical applications for the management of melanoma patients, since the gp75 antigen is conserved from mouse to man,” says researcher Dario Neri, Ph.D., Swiss Federal Institute of Technology, Switzerland.

Previous research has demonstrated that simultaneous intravenous administration of B16 melanoma cells and the gp75-specific TA99 antibody in murine IgG2a format could efficiently prevent formation of lung metastases in mice.2 However, further studies found that IgG2a(TA99) could not eradicate melanoma lesions once the tumors had established as small subcutaneous solid nodules.3,4,5

The Swiss researchers set out to characterize the tumor-homing properties and therapeutic activity of murine IgG2a(TA99) and investigate whether antibody-dependent cell cytotoxicity (ADCC) could be potentiated.

They found that the therapeutic activity of IgG2a(TA99) could be substantially enhanced by co-administration with an antibody cytokine fusion (TA99-mTNF), consisting of the TA99 antibody in scFv format fused to murine TNF. This fusion protein efficiently killed endothelial cells in vitro, while displaying only minimal activity against B16 melanoma cells.

In vivo, TA99-mTNF boosted the influx of natural killer (NK) cells and macrophages into B16 melanoma lesions.

“Therapy studies with two different administration schedules revealed that the combination of TA99-mTNF and IgG2a(TA99) was superior to the individual products used as single agents,” Dr. Neri says. “The combination treatment converted most of the tumor mass into a necrotic lesion, but a vital tumor rim eventually regrew, even when dacarbazine was included in the therapeutic regimen.”

There has been intense effort in potentiating the ADCC activity of antibodies by mutagenesis of the Fc portion or glycoengineering, and the use of antibody-cytokine fusions, capable of boosting the influx and activation of certain leukocytes into the tumor cells mass, may represent a valuable complementary approach, he explains. “While two TNF fusions are currently being investigated in advanced clinical trials, we are not aware of on-going combination trials with IgG based therapeutics.”

In preclinical cancer models, the main activity of targeted TNF products appears to be associated with a rapid induction of hemorrhagic necrosis, and in patients similar effects on superficial melanoma lesions have been reported in isolated limb perfusion procedures both with recombinant TNF and with the L19-TNF fusion.

Dr. Neri says: “ADCC remains an attractive and elegant avenue for exploiting the potential of the immune system, against target antigens of choice. Biocidal events are only manifested when the IgG molecule engages in a binding

“... These findings may open new clinical applications for the management of melanoma patients.”  Dario Neri, Ph.D., Swiss Federal Institute of Technology, Switzerland
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INDICATION
ALTRENO™ (tretinoin) lotion, 0.05% is indicated for the topical
treatment of acne vulgaris in patients 9 years of age and older.

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

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

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

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Customer
Service at 1-800-321-4576 or the FDA at 1-800-FDA-1088 or
fda.gov/medwatch.

Please see Brief Summary of Prescribing Information on
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ALTRENO™ (tretinoin) lotion, for topical use

Initial U.S. Approval: 1973

INDICATIONS AND USAGE

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

CONTRAINdications

None.

WARNINGS AND PRECAUTIONS

Skin Irritation

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

Ultraviolet Light and Environmental Exposure

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

Fish Allergies

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ALTRENO N=767</th>
<th>Vehicle N=783</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site dryness</td>
<td>29 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>25 (3)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>12 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>7 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Application site exfoliation</td>
<td>6 (1)</td>
<td>3 (&lt;1)</td>
</tr>
</tbody>
</table>

Application site pain defined as application site stinging, burning or pain.

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ALTRENO N=760 Mild/Mod/Severe</th>
<th>Vehicle N=782 Mild/Mod/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Scaling</td>
<td>49%</td>
<td>30%</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Itching</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Burning</td>
<td>30%</td>
<td>14%</td>
</tr>
<tr>
<td>Stinging</td>
<td>21%</td>
<td>8%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Data

Human Data

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

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

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

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).
Fat intake linked to skin cancer risk

ILIYA PETROU, M.D. | Staff Correspondent

The association between dietary fat intake and the development of certain types of cancers including colorectal, breast, and prostate has been well established. The results of a recent study investigating the association between dietary fat intake and the development of skin cancers were mixed but found polyunsaturated fat intake especially omega-6 fat to be modestly and consistently associated with skin cancer risk.

“As there have been few epidemiologic studies of fat intake and skin cancer, our findings on specific types of fat intake and skin cancer need to be replicated in other populations before we advise patients based on their fat intake. Until we get more data from other populations, people should follow well-established prevention guidelines for skin cancer such as reducing sun exposure,” said Eunyoung Cho, M.D., department of dermatology, Warren Alpert Medical School of Brown University, Providence, RI.

In the prospective study, Dr. Cho and fellow researchers investigated the potential association between dietary fat intake and the risk of skin cancer including cutaneous malignant melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) evaluating the combined data from the Nurses’ Health Study (NHS 1984-2012) and the Health Professionals Follow-up Study (HPFS 1986-2012), two prospective studies in which the dietary information regarding the consumption of total and types of fat including saturated, monounsaturated, polyunsaturated, omega-6, and omega-3 fat and cholesterol was regularly assessed and recorded approximately every 4 years. Incident cases were identified by self-report.

A total of 794 melanoma, 2,223 SCC, and 17,556 BCC cases, and 736 melanoma, 1,756 SCC, and 13,092 BCC cases were found in the NHS and HPFS studies, respectively. No association between total fat intake and risk of skin cancer was identified in the two prospective studies. Data showed that the risk for developing SCC and BCC was associated with a higher intake of polyunsaturated fats. While the risks of SCC, BCC, and melanoma were associated with a higher omega-6 fat intake, omega-3 dietary fat intake was found to be associated with risk of BCC but not with SCC or melanoma. No other fats were associated with melanoma risk. Interestingly, higher cholesterol and monounsaturated fat intake was associated with lower risk or SCC and BCC, respectively. The associations on the whole were also found to be similar in women and men and by other skin cancer risk factors.

Animal studies have shown the tumor promoting effects of omega-6 fat on UVR-induced carcinogenesis. According to Dr. Cho, one theoretical biological mechanism is that omega-6 fat intake may increase pro-inflammatory and immunosuppressive prostaglandin E synthase type 2 levels, which is associated with aggressive growth patterns of non-melanoma skin cancer (NMSC).

“Our study suggests potential effect of diet on skin cancer development, which needs to be further explored in other populations. Avoiding sun exposure is still the best strategy to prevent skin cancer,” Dr. Cho said.

Disclosures: Dr. Cho reports no relevant disclosures.

References

Skin rash post target therapy may be ‘cytokine storm’

INGRID TORJESEN | Staff Correspondent

A round one in five melanoma patients treated with BRAF/MEK inhibitors after previous immunotherapy present with a severe skin rash (grade ≥3), which may be complicated by systemic involvement and organ damage.1

It has been previously suggested that those with kidney, liver, and heart involvement experience a systemic reaction—drug rash with eosinophilia and systemic symptoms (DRESS)—but now researchers writing in a letter to the journal Melanoma Research have proposed that patients experience a “cytokine storm” and that their symptoms are actually due to cytokine release syndrome (CRS).2

The research group has previously reported four cases of cytokine release syndrome (CRS) following the use of BRAF/MEK inhibitors after immune checkpoint blockade with severe (grade ≥3) skin and systemic involvement.3,4 “The pattern of the symptoms—pyrexia and maculopapular rash, and also transaminities (an uncommon event during treatment with BRAF/MEK inhibitors)—fulfills the diagnosis of a cytokine release syndrome, says one of the researchers Reinhard Dummer, M.D., University Hospital of Zurich, Switzerland. “The documented, high circulating cytokine levels, including interleukin-6 (IL-6), tumor necrosis factor-α, and interferon-γ, further confirm our hypothesis,” he said.

Such episodes have also been reported in the preliminary findings of a phase three clinical trial with dabrafenib, trametinib, and an anti-PD1 antibody.3

Dr. Dummer points out that these cases are distinguished from a hypersensitivity reaction to the kinase inhibitors (DRESS) as they lack of frequently observed eosinophilia, other blood abnormalities, reactivation of human herpes virus, or lymphadenopathy do not support the diagnosis. The short onset of symptoms after treatment initiation (around 10 days) and the tolerance of the identical medication after reinduction are also typical for a systemic inflammatory reaction and untypical for DRESS, he adds.

“We attribute this systemic reaction to an aberrant release of proinflammatory cytokines, mainly accompanied by symptoms such as pyrexia, transaminities, renal insufficiency, and maculopapular skin rash,” he says.

The high level of immune activation in the context of simultaneous inhibition of checkpoint and MAPK pathway inhibition means a ‘cytokine storm’ is a possible mechanism for CRS. Dr. Dummer suggests. “Oncogenic drivers in the immune system leads to a T-cell activation and consecutive release of cytokines, such as tumor necrosis factor-α and interferon-γ, with further activation of innate immune cells and production of numerous cytokines, among all also IL-6, which importantly causes a positive feedback loop, leading to a ‘cytokine storm. However, clinical and preclinical data propose that MAPK pathway inhibition may enhance T-cell activation through an increase of proinflammatory cytokines and cytotoxic factors. These changes to the tumor microenvironment would be expected to increase efficacy by making tumors more susceptible to immunotherapy.”

The management and treatment of the CRS can be very challenging. “We advise the practitioners to measure the cytokine levels and use cytokine antagonists as potential therapeutic candidates in cases refractory to steroids,” Dr. Dummer says. ◄

References


Quick TAKES

One in five melanoma patients treated with BRAF/MEK inhibitors post immunotherapy develop a severe rash.

A high level of immune activation with checkpoint and MAPK pathway inhibition indicates presence of a cytokine storm.

Cytokine antagonists may lessen the severity of the rash.
TRIM29: New target in SCC treatment?

NAVEED SALEH, MD, MS | Cancer Network

**Quick Takes**

**TRIM29**

Seems to regulate keratin distribution and SCC migration/invasion.

- **TRIM29 has been linked to breast, colorectal and pancreatic cancers.**

- **Survey suggests upregulated TRIM29 expression predicted poor prognosis in patients with malignant neoplasms.**

- **TRIM29 is highly expressed in stratified head and neck epithelial tissues.**

The tripartite motif-containing protein 29 (TRIM29)–keratin axis could become a potential new drug target in the treatment of squamous cell carcinoma (SCC), according to a recent study published in *Cancer Research*.

“Our findings reveal a critical function of TRIM29 in regulating keratin distribution as well as migration/invasion of SCC,” wrote the authors, led by Teruki Yanagi, MD, PhD, a faculty member in the Department of Dermatology at Hokkaido University in Japan.

TRIM family proteins function in various ways during cellular processes, including intracellular signaling, cell development, protein quality control, apoptosis, and carcinogenesis. A member of the TRIM family of proteins, TRIM29, has been linked to breast, colorectal, and pancreatic cancers.

A recent survey of TRIM29 in a range of cancers suggested that upregulated TRIM29 expression predicted poor prognosis in patients with malignant neoplasms. However, its role in SCC is currently unknown. Searches of public databases revealed that TRIM29 is highly expressed in stratified epithelial tissues found at the level of the head and neck.

In the current study, Yanagi et al analyzed TRIM29 expression in cutaneous head and neck squamous cell carcinomas (SCC), as well as its tumorigenic roles.

The researchers observed that TRIM29 expression was lower in malignant SCC lesions compared with adjacent normal epithelial tissue or benign tumors. This decreased TRIM29 expression correlated with higher SCC invasiveness.

Primary tumors of cutaneous SCC demonstrated aberrant hypermethylation of the Cpg lesion of TRIM29. In a related finding, TRIM29 expression in these tumors was also associated with the altered keratin expression and distribution. The team also found that depleting TRIM29 heightened the migration of cancer cells, whereas TRIM29 overexpression subdued this migration.

Utilizing non-biased comprehensive proteomics and immunoprecipitation analyses, Yanagi et al identified keratins and the keratin-interacting protein FAM83H as TRIM29 interactors. Finally, the investigators discovered that the RNAi-mediated gene-knockdown of TRIM29 led to ectopic keratin localization of keratinocyes.

“We revealed an unrecognized role of TRIM29 in the cell migration/invasion of cutaneous and head/neck SCC tumors,” the authors concluded. “The present results suggest that TRIM29 could be a novel diagnostic/prognostic marker in stratified epithelial tumors. Also, the TRIM29-keratin axis may be a novel therapeutic target in intractable/metastatic SCCs.”

In an interview with *Cancer Network*, dermatologist Jerry D. Brewer, MD, MS, a dermatologist and professor of dermatology at the Mayo Clinic, considered the potential implications of the study. “This is an interesting study, the findings of which may spur further research or even drive treatment strategies in the future for cutaneous SCC.”
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Aesthetic advances

Physicians share which trends may be most impactful in 2019

LISETTE HILTON | Staff Correspondent

One of the most exciting things about greeting the New Year is the anticipation of what’s next for the aesthetic industry. Therefore, we asked several aesthetic doctors to offer their perspective on trends that could impact aesthetic physicians and their patients in 2019. Here’s what each had to say.

SOCIAL INFLUENCERS RALLY

“Increasingly decisions about appearance, cosmetic procedures and skincare, etc., are being affected by social media influencers,” according to Mary Lynn Moran, M.D., president-elect of the American Academy of Facial, Plastic and Reconstructive Surgery (AAFPRS).

While the Hiltons and Kardashians are among the original social media influencers, just about anybody who has a significant following on Instagram, Facebook or other social media platforms can influence. Those with a large following are sometimes getting paid to promote anything from what kind of grapes they eat to what filler they’re using, Dr. Moran says.

“Everything is documented and sometimes monetized,” she says.

Some aesthetic physicians are positioning themselves as social influencers by posting procedures, results and even personal pictures. They’re also partnering with influencers and sometimes offering treatments in exchange for the influencers’ social media exposure. Influencers don’t always disclose if they’re getting what they promote for free or at a reduced rate. The information is being presented in a very compelling and relatable way but patients aren’t always in a position to determine the accuracy or bias of the information presented.

On the positive side, by posting procedures and promoting cosmetic procedures, social influencers are reducing fear associated with cosmetic treatments.

“It’s making treatments seem more accessible and normalizing it. On the one hand, it’s good because people are being educated — albeit in a way that’s sponsored in some cases,” she says. “I would say that’s probably lowering the threshold for younger people — as well as for men — to have procedures done.”

Dr. Moran says she believes the trend will continue to grow.

COMEBACK PROCEDURES

Dr. Moran says the surgical lip lift is getting new life among aesthetic patients.

“People are becoming a little disenchanted with fillers, and they don’t always work the way you want them to,” she says.

The desire for a more permanent solution is propelling the popularity of the outpatient surgical lip lift, according to Dr. Moran.

And thread lifting, which came and went a few decades ago, is back because the technology is more refined, she says.

NEW TAKE ON INJECTABLES

“There are definitely going to be some longer lasting neurotoxins,” Dr. Moran says.

Some aesthetic physicians are...partnering with influencers and sometimes offering treatments in exchange for the influencers’ social media exposure.
"Smaller amounts of injectables early on and on a more regular basis is becoming more of a trend."

Mary Lynn Moran, M.D., president-elect of the American Academy of Facial, Plastic and Reconstructive Surgery

RT002 (daxibotulinumtoxinA, Revance Therapeutics) is among today’s pipeline neurotoxins. Revance plans to file a Biologics License Application the first half of 2019, according to a public relations person representing the company.

“There will be some new hyaluronic acid fillers,” she adds. “They’re all just variations on the same theme but I think they will continue to improve.”

Dr. Moran says micro doses of both fillers and neurotoxins are trending.

“Some practitioners are diluting neurotoxins or hyaluronic acid and then putting it in a little stamper device and injecting it. That’s supposed to help with pores and fine wrinkles. There’s also a technique where you inject smaller amounts throughout the skin using a needle,” she says. “Smaller amounts of injectables early on and on a more regular basis is becoming more of a trend.”

SAFETY IN 2019

Safety will be the mantra in 2019, fueled by international news coverage of the dangers of fat grafting of the buttocks.

“The industry is really trying to wrap its head around the best way to afford patients those kinds of outcomes but with a safety profile that’s more reasonable for elective cosmetic surgery,” says Alexander W. Sobel, D.O., president of the American Board of Cosmetic Surgery.

To a lesser degree, discussions about safety will also arise from the rare but headline-making cases of anaplastic large cell lymphoma associated with breast implants, he says.

The ripple effect could reduce demand for the Brazilian butt lift and even

MICRO DOSES CONTINUES ON PAGE 60>

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**IMAGING EXCELLENCE FROM CANFIELD**
Micro doses of both fillers and neurotoxins are trending. From Page 59

Breast augmentation, but Dr. Sobel admits patient demand for these procedures seems unflappable. He thinks the spotlight on safety might help educate the public about potential dangers of going to inexperienced or unqualified providers for cosmetic treatments.

“I hope the fallout is something very positive where the public and physicians have very open discussions about facility accreditation and the sorts of environments of care in which these procedures are taking place,” he says.

Biologically Active Fillers
Today’s burgeoning array of synthetic fillers have their places in facial rejuvenation. What they don’t do well is biologically improve skin or tissue for long-term results. That’s where biologic products come in, and 2019 could be the year those injectables become available, Dr. Sobel says.

“The inflammation that’s created by fillers does help, but you’re not really donating stem cells or any other biologically competent body products that can help in the long-term from an antiaging standpoint,” he says. “Allergan has gotten interested in fat grafting recently but has been very quiet about it. My hope is that we’ll start seeing more conversation about the role of biologically active fillers, particularly fat grafts to the face, platelet rich plasma, a variety of other human derived products that could be tremendously helpful in the antiaging armamentarium.”

Hair Restoration Revival
Dr. Sobel thinks demand for hair restoration will increase like a tidal wave over the next few years.

“Devices like the NeoGraft and others are making hair transplantation much more economical and effective, with a lower side effects profile. If you do all three of those things simultaneously, you can’t help but have a big uptick in the volume of patients treated,” he says.

Less Laser Risk
There’s always something new in the laser and light device market, but the industry has yet to get a real handle on pigmentary disorders and understanding how laser and light therapy can exacerbate them, Dr. Sobel says.

Two big trends in cosmeceuticals

By Lisette Hilton

Trending in cosmeceuticals for 2019: products that are organic and microbiome friendly, according to dermatologist Zoe Diana Draelos, M.D., who practices in High Point, N.C., and founded dermatology Consulting Services, a company that works with cosmeceutical firms to develop formulations and conduct product testing.

Organic, Please
Consumers want more than organic food; they want organic skincare, including “natural” ingredients that are sustainable and plant-based, as well as products free of petroleum distillates, including petroleum jelly and mineral oil, according to Dr. Draelos.

Next to product claims, such as hypoallergenic, noncomedogenic and non-acnegenic, companies are adding organic, natural and sustainable, she says.

But the reality is that claiming a product is natural could mean it contains anything found on the earth. Many consumers’ expectation is that natural ingredients are plant-derived, according to Dr. Draelos.

“Bad” ingredients are silicone, because while it comes from sand it’s not naturally available and has to be made, and petroleum distillates, because crude oil comes from the ground but has to be distilled in order to get the various fragments,” Dr. Draelos says. “People are eliminating these supposed bad ingredients and trying to find similar plant-based substances.”

Focusing on the Microbiome
The trend in 2019 is to develop skincare products that don’t damage the microbiome, according to Dr. Draelos.

“You’re going to see a lot of cosmetic products and cosmeceuticals stating that they’re microbiome friendly. That’s an interesting twist because no one was ever previously concerned about preserving the bacteria on the skin’s surface,” she says.

The concept is to choose a preservative that would be in a concentration low enough to kill bacteria without theoretically affecting the microbiome.

Manufacturers also are looking at ways of enhancing and normalizing the microbiome, while pushing out disease-causing organisms.

“For example in acne, there are many different strains of Propionibacterium acne. Some are more pathogenic; some are less pathogenic. But the idea would be to put a product on your face that would allow bacteria, such as lactobacillus, to populate the face, crowding out the Propionibacterium acne thus allowing acne to get better,” she says.

The two diseases that are most interesting in this space are atopic dermatitis, because the aim is to push out Staphylococcus aureus and acne, where the products would try to push out pathogenic strains of Propionibacterium acne.

“It would be like putting a yogurt type solution on your face to try and repopulate your face or your body (in the case of atopic dermatitis) with nonpathogenic bacteria—getting rid of the pathogenic bacteria not by destroying them, like you would with an antibiotic, but by crowding them out because every bacterium has to have a piece of skin to live on,” Dr. Draelos says.

“The idea is to colonize your skin with non-disease-causing organisms and to crowd out the bacteria that cause disease—basically starve them out, because there’s no real estate on the skin’s surface on which they can grow.”
skin medications, like hydroquinone, to reduce that risk and enhance results. pigmentation from treatment and putting patients who are at risk on topical use the devices more sensibly by educating patients about the risk of hyper-want.”

NuBody has a potential effect on the appearance of cellulite, according to an FDA-cleared microcurrent device that helps tone and firm body skin. with the at-home DermaFlash 2.0, according to Dr. Schlessinger. frequency for medical practices, which can be used alone or in conjunction aates and gets rid of peach fuzz, should be a big seller in 2019. Soon, the company plans to introduce a similar technology using radio-frequency for medical practices, which can be used alone or in conjunction with the at-home DermaFlash 2.0, according to Dr. Schlessinger. He’s also excited about the new at-home NuBody device (NuFace). It’s an FDA-cleared microcurrent device that helps tone and firm body skin. NuBody has a potential effect on the appearance of cellulite, according to Dr. Schlessinger.

“I’d like to see more safety,” he says. “Laser light is sexy. It’s what patients want.”

Dr. Sobel says the solution is a treatment paradigm in which physicians use the devices more sensibly by educating patients about the risk of hyperpigmentation from treatment and putting patients who are at risk on topical skin medications, like hydroquinone, to reduce that risk and enhance results. COMPETITION AND VALUE FOR THE CORE INJECTOR With the likely addition of one or two new neurotoxins, there will be more competition in an already crowded provider marketplace, according to Joel Schlessinger, M.D., a dermatologist and cosmetic surgeon practicing in Omaha, Neb. “This will provide more options for dermatologists and cosmetic surgeons to provide for their patients. And it will further cement the importance of relationships between companies and dermatologists and cosmetic surgeons,” he says. Dr. Schlessinger says increasing outreach to “non-qualified practitioners” to get sales is putting significant strain on physicians’ relationships with these companies. “You see many people who are touted as adequate or approved injectors and this alone could be a reason to switch to a new company that might provide a better value for the core injector (dermatologist, plastic surgeon, ocularplastic and facial plastic),” Dr. Schlessinger says.

CELLULITE OPTIONS GO MAINSTREAM Dr. Schlessinger says Cellfina (Ulthera) is his number one pick for treating cellulite. “But I still feel the public has no clue that cellulite is essentially a problem that is treatable,” he says. “Clearly there are areas where Cellfina can’t be used — the banana roll area and more severe cases of cellulite — but it truly is something that has made a huge difference in many people’s lives and has long-term if not extraordinarily long-term results.”

Dr. Schlessinger says he thinks new cellulite treatments in 2019 could help push these options to the mainstream.

AT-HOME DEVICE DEMAND Dr. Schlessinger says the DermaFlash 2.0 (DDK DRTV), which is the next generation of the popular DermaFlash at-home device that exfoliates and gets rid of peach fuzz, should be a big seller in 2019. Soon, the company plans to introduce a similar technology using radio-frequency for medical practices, which can be used alone or in conjunction with the at-home DermaFlash 2.0, according to Dr. Schlessinger.

He’s also excited about the new at-home NuBody device (NuFace). It’s an FDA-cleared microcurrent device that helps tone and firm body skin. NuBody has a potential effect on the appearance of cellulite, according to Dr. Schlessinger.

“These devices seem to capture the public’s imagination,” he says.

PATIENT EXPECTATIONS The public’s increasing reliance on social media images continues to create illusions about what can actually be achieved. And they often turn to nonsurgical options to when, in certain cases, that may not be the right choice, says Philip R. Langsdon, M.D., president of the American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS). “With that trend, there are more people who undergo nonsurgical treatments and only later discover that fillers cannot actually provide the same results that can be obtained with a facelift. You can’t lift sagging tissue by using fillers or various machines,” Dr. Langsdon says.

“So, the public is becoming more aware. For instance, they’re beginning to understand that if you have sagging tissue, you’re going to have to have surgery. If your face is defl ating, you’re going to need some volume from somewhere, whether it comes from off-the-shelf fillers or fat. And they’re learning that the wrinkles aren’t going to go away with any of these treatments, you’re going to need some sort of resurfacing procedure, such as a laser or chemical peel. To make it even more complicated, there are various kinds of lasers and peels that provide different results.”

YOUNG PATIENT EXPECTATIONS There is increasing demand among younger patients for light chemical peels, laser and light treatments and filler and neuromodulator injections. More young patients, according to Dr. Langsdon, also are coming in for surgical rhinoplasty. Aesthetic surgeons should be sure to set realistic expectations because many young rhinoplasty patients have unrealistic expectations.

PATIENT REVIEW Concerns “I think there is a growing concern among providers about patient responses and ratings,” says Dr. Langsdon.

While he says that he doesn’t know how the problem might resolve in 2019 and beyond, Dr. Langsdon says there are no safeguards that help to ensure the reviews are credible and reflect reality. And they can unfairly tarnish doctors’ reputations. ▲

Disclosures: Dr. Schlessinger founded and owns the online skincare marketplace LovelySkin.com. Drs. Meron, Sobel and Langsdon report no relevant disclosures.
Aesthetic medicine: Marketing by generation

LISETTE HILTON | Staff Correspondent

Quick Takes
Older generations care about reviews more than price.

Gen Y, Z respond to robust online content and mobile-friendly sites.

Word of mouth remains most effective across generations.

Generations of people tend to share characteristics that aesthetic practices can harness to better target their marketing efforts. From social media to billboards to, yes, even television, the right mix can optimize marketing to today’s generations:

- Traditionalists, also known as the silent generation, born between 1922 and 1945
- Baby boomers, born between 1946 and 1964
- Generation Xers, born from 1965 to 1979
- Millennials, born between 1980 and 1995
- Generation Z, born after 1995

So what are the important generational differences and how can that information be used to build successful marketing campaigns? Industry physicians, marketing experts and researchers advise.

The Older Generations
While members of the silent generation might be less accustomed to communicating electronically, baby boomers are versatile in their communication and are more likely to embrace online and social media marketing. Still, these older generations tend to respond to traditional marketing approaches, such as sponsoring and participating in community events — from fun runs to food drives, according to Joe Sloan, marketing and communications coordinator at Advice Media.

As consumers and patients, baby boomers care about reviews, referrals and looking for the right person. They don’t tend to be price sensitive, according to Tom La Vecchia, M.B.A., president of X Factor Media.

Generation Xers
Generation Xers often make up large percentages of the aesthetic practice’s patients. One way to reach this generation is through referral programs, according to Sloan.

“This is a great way to attract new patients and reward your most loyal patients,” Sloan says. “You want to provide a system that will encourage word-of-mouth marketing by rewarding both the referrer and referee. Referrals are one of the most trusted marketing sources.”

Gen Xers tend to be price sensitive but will be loyal to a provider if providers meet their needs, according to Mr. La Vecchia.

Millenials
Millenials, or generation Y, grew up on the internet and expect to find answers quickly no matter the device, Mr.
Sloan says. They are inquisitive. They grew up on text messages, emails and instant messages, and expect quick feedback.

Millenials want value, care about social proof and need to like the provider above and beyond the service. In other words, experiences matter, according to Mr. La Vecchia.

Aesthetic practices trying to reach millennials should have fast, mobile-responsive websites that work on phones, tablets and computers. The next step is to optimize content on the site to appear higher in Google Search results, according to Mr. Sloan.

GEN Z

Generation Z is a generation that expects you to be there when they’re looking.

“This generation doesn’t respond to being advertised at or outbound marketing as much as it does to inbound marketing. This means they don’t want you to advertise to them. They want to find you,” according to Mr. Sloan.

Practices should focus on having robust content that answers potential patients’ questions at any stage in the decision-making process.

According to Mr. Sloan, this means that practices should offer detailed information during the awareness stage, feature a before and after gallery when people are in the consideration stage, and provide pricing and contact information for the decision stage.

Demonstrations appeal to Gen Z patients. They crave information before making aesthetic decisions and want to feel educated. They’re a bit more frugal than millennials, according to Mr. La Vecchia.

Generation Z, also called the “new silent generation,” loves YouTube, Mr. Sloan adds.

“This is a generation that is very familiar with searching for videos from ‘How To’ to lifestyle vlogs. …you will want to make sure your practice has videos that are well produced and help to answer questions these potential patients may be too embarrassed to ask,” Mr. Sloan says.

APPLYING KNOWLEDGE TO PRACTICE

Inessa Fishman, M.D., a facial plastic and reconstructive surgeon in Atlanta, Ga., says her patients are multigenerational.

“While my aging face practice tends to be 40s and older, my injectables and rhinoplasty patients are usually in the teens [to] young 30s crowd,” Dr. Fishman says.

The marketing strategies that resonate with Dr. Fishman’s younger patients include a mix of the old and newer marketing approaches.

Word of mouth remains king, according to Dr. Fishman.

“Nothing is a stronger recommendation than a close girlfriend or sister or Barre classmate,” according to Dr. Fishman. “I have a yoga teacher whose clients I see at least every week. The influencers are now influencing in person and on social media. …a recommendation over coffee goes alongside a shout-out on [Instagram, or IG].”

RealSelf and Instagram are more popular than ever, she says.

“My younger patients are spending less time on Facebook and are Instagramming multiple times a day. I feel that IG content needs to be beautiful, curated, visually interesting and able to convey a strong message in less than 30 seconds,” she adds.

“RealSelf is very popular in my practice and brings in younger patients who are using it to vet both procedures and physicians. I’m also seeing Pinterest rise in popularity, both in the 20-year-old women and young moms.”

And before and after photos might be losing ground to videos, according to Dr. Fishman, who says videos resonate with younger patients. These include videos about procedures, patient testimonials and before and after videos.

“Sleek productions, tailored content, beautiful fonts — these are all becoming more accessible to everyone in the industry, and the quality of content is truly better than ever,” Dr. Fishman writes. “I also see more personal ‘a glimpse into my life’ posts being more popular with my patients.”

San Francisco-based plastic surgeon Jonathan Kaplan, M.D., MPH, says that to reach generations X and Z and millennials, his practice is very active on social media. They post his surgeries on Snapchat and as Instagram stories. Doing so captures teenagers to 40-something year olds, he says.

But his approach to 50-something and older patients is to market via billboards and television commercials. Yes, he says, people are still watching TV!

SOCIAL MEDIA BEST PRACTICES

Aesthetic practices should keep three steps in mind when using social media to market to the generations, according to Mandy McEwen, founder and CEO of Mod Girl Marketing:

1. Choose the right channels.
2. Choose the right messaging.
3. Choose the right follow-up methods.

While Snapchat and Instagram can be ideal platforms for reaching millennial and generation Z patients, silent generation patients are more likely to be on Facebook, according to Ms. McEwen.

“Choosing the right channels is just one step of devising a successful, segmented marketing strategy. You must also convey the right messaging,” McEwen says.

“A 21-year old uses different language and has different interests than a 65-year old. A 21-year old also values social proof and is constantly looking for what their peers are saying and doing.”

For follow-up, McEwen says that the younger generation of patients often prefers text messages over phone calls.

“Of course, having a combination of text, phone calls, and emails is the best way to ensure you are reaching your prospects via every possible channel, as long as it’s done strategically and not intrusively,” says McEwen.
Dermatology care for women goes beyond skin. Practicing dermatologists reside at the crux of meeting women’s needs, said Pearl Grimes, M.D., president of Women’s Dermatologic Society (WDS).

“We play a role in addressing issues, such as aging, self-esteem, hormones, and stress management. We look at all of these things, but it comes through dermatology,” she said. “We’re such integral players in the house of medicine. As part of that total health team, we particularly look at the total health of women.”

WDS launched an initiative this spring to help fulfill this responsibility. The program, known as Total Women’s Health Through the Dermatology Gateway, offers providers the education and tools necessary to maximize their critical patient care responsibilities.

To help both male and female dermatologists reach this goal with their female patients, the Gateway includes educational support, community intervention, and industry research leadership possibilities through the International Journal of Women’s Dermatology.

According to Jenny Murase, the Journal’s co-editor-in-chief, the Gateway initiative presents the opportunity for dermatologists to make a long-term impact on women’s health.

“When we play a role in addressing issues, such as aging, self-esteem, hormones, and stress management, we look at all of these things, but it comes through dermatology,” she said. “We’re such integral players in the house of medicine. As part of that total health team, we particularly look at the total health of women.”

WDS launched an initiative this spring to help fulfill this responsibility. The program, known as Total Women’s Health Through the Dermatology Gateway, offers providers the education and tools necessary to maximize their critical patient care responsibilities.

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“When skin, hair, and nails are critical elements under the Total Women’s Health umbrella, and we need dermatologists at the table to represent these important facets of health during a woman’s journey, ranging from childhood, adolescence, child-bearing years, and including episodes of pregnancy, breastfeeding, and menopause,” she said.

MULTI-DISCIPLINARY EDUCATIONAL OPPORTUNITIES

Before the Gateway, Dr. Grimes said, WDS had never offered any continuing medical education (CME) opportunities. The first event is scheduled for February 2019 and will offer traditional leadership and mentoring programs. However, it will also include sessions and discussions with women physicians from other specialties, including cardiology, gynecology, psychiatry, and others.

“These women will spend the morning talking about the total women’s health issues we see and address in our patients through the dermatology gateway via discussions with our patients and referrals,” she said.

More dermatology-specific topics, such as skin cancer management, latest developments in alopecia, and atopic dermatitis, will fill the afternoon.

Ultimately, she said, she hopes the CME event will impress upon dermatologists that, in many ways, they are part of the first line of defense when it comes to fulfilling a patient’s health needs.

“It’s about addressing the needs of the total woman rather than just her skin care needs,” Dr. Grimes said. “We don’t expect dermatologists to be cardiologists or psychiatrists, but they need to get a sense of where she is and let her know you’re an integral player on her team.”

To continue this work, she said, the WDS will apply for grants that will support their quest for a greater volume of evidence-based data on women’s health issues and how they can be met through the Gateway.

REACHING THE COMMUNITY

Not every woman has easy access to dermatology services, Dr. Grimes said. To help meet their needs, dermatologists participating in the Gateway initiative are already taking their services to women’s health.

Currently, there are two women’s shelter programs operating—one in Los Angeles and one in Lafayette, La., but WDS plans to open between 10 and 13 programs within a year.

“Every component of this program is geared toward building self-esteem in women in shelters so when they re-emerge into the real world, they’re re-emerging with a much stronger sense-of-self, self-esteem, and empowerment,” she said.

During these Saturday sessions, dermatologists offer guidance about skin care-on-a-budget, nutrition-on-a-
budget, social skills and etiquette training. For example, women learn about quality cleansers and moisturizers available for less than $10, as well as the importance of sunscreen for preventing skin cancer and Vitamin D supplements for women of color.

Additionally, she said, these sessions provide information about good nutrition to improve overall health. The dermatologists leading the groups pass out healthy meal planning brochures and discuss how genetically-modified foods, high-and low-glycemic index foods, healthy snacks, and how to avoid toxins present in canned foods.

**RESEARCH LEADERSHIP**

Although in-office and community interactions are important, passing along evidence-based research about the role and impact of dermatologists in women’s health is also vital, Dr. Grimes said. Consequently, the *Journal* has augmented the topics it will cover in two sections.

“We developed the Women’s Health Highlight and the Patient Pages to highlight topics that have broad appeal for the general population,” the *Journal* editor said.

The Women’s Health article will be the first article every month and will address subjects that touch both dermatology and other specialties. They will be either reports, evidence-based reviews, studies, or opinions pieces. Subjects will cover a wide gamut with two of the first articles focusing on cosmetic procedures safe during pregnancy and vaginal rejuvenation.

According to Murase, the Patient Pages will be printable information that dermatologists can use to prompt their patients to ask relevant questions and begin dialogues.

Ultimately, Dr. Grimes said, she hopes the Gateway initiatives breathe new life into how dermatologists approach caring for their female patients.

“Our hope is that women dermatologists will understand the need and importance of addressing the total issues that women face in their overall health,” she said. “It’s about counseling and about getting women the appropriate referrals. The takeaway message is that you can have tunnel vision. You have to view the patient — and taking care of their skin — as being part of whole health.”

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**2018 YOUNG LEADERS**

The DF Board of Trustees is pleased to recognize the following individuals for their decision to join their colleagues in leadership giving within five years of completing their dermatology residency. Each has made a commitment that will support innovative research and advancements in treatments that will benefit patients everywhere. Their decision to take an active role in shaping the future of the specialty early in their careers is deeply appreciated.

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Aaron Mangold, M.D.
Katie Mercy, M.D.
Andrea Morris, M.D.
Melissa Muszynski, M.D.
Anne Neeley, M.D.
Caroline Nelson, M.D.
Hogan Roe, M.D., M.P.H.
Alex G. Ortega-Louyza, M.D.
Erik L. Peterson, M.D.
Evan Pellegrini, M.D.
Francisco Ramirez-Vall, M.D., Ph.D.
Bahram Razavi, M.D., Ph.D.
Roberto R. Rios-Gonzalez, M.D., Ph.D.
Emily Stammel Ruiz, M.D.
Rachel A. Scheinert, M.D.
Steven Schuckit, M.D.
Cory L. Simpson, M.D., Ph.D.
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Sklar Souther, M.D.
Abigail L. Taft, M.D.
Dana Trell, M.D.
Amanda R. Tidwell, M.D.
George Varghese, M.D.
Kara Walton, M.D.
Cameron West, M.D.
Kelly Morrissey Williams, M.D.
Lindsay H. Wilson, M.D.
Hajie Ye, M.D.
Amanda Zobek, M.D., Ph.D.
Navigating the reimbursement landscape can be confusing for physicians because of the number of entities that exert influence on payments. For example, CMS uses the Medicare Physician Fee Schedule (PFS) to adjust Medicare payments, and sometimes these changes can have dramatic effects on doctor pay. Coding changes reward some types of care while de-emphasizing others through how much reimbursement is allowed for each. In addition, the MIPS program is pushing Medicare into value-based care, distributing bonuses and penalties to doctors depending on how well they meet various quality measures.

Many private payers also use quality metrics, but often, these are somewhat different from those that CMS uses and from each other’s. And to top it all off, all these rules can change each year. So what reimbursement trends can physicians expect in 2019?

MIPS BONUSES AND PENALTIES

For physicians using the “ignore it and hope it goes away” strategy for MIPS, 2019 might provide a rude awakening as bonuses and penalties based on 2017 claims data go into effect.

“The concept of MIPS will not go away, and even if it did, it would just be replaced by something similar,” says Anders Gilberg, MGA, senior vice president, government affairs, for the Medical Group Management Association. “It is one of the few bipartisan-supported concepts in healthcare today.”

The payment adjustments for this year are relatively small—2% is the maximum bonus and 4% the maximum penalty, depending on how a physician did on the performance measures in 2017. While that might not have much effect on a practice’s financial situation this year, those adjustments are scheduled to increase to 7% in 2021 and 9% in 2022 and beyond. “Practices have the opportunity to receive a higher increase in 2021 than previous years based on what they do in 2019,” says Gilberg. “But they could also see a significant penalty.”

CMS reported that 93% of MIPS-eligible clinicians earned a payment bonus for 2019, but 2017 was a “pick your pace” year to introduce physicians to the program. As performance measures change—and cost containment becomes a bigger component of the score—fewer physicians are likely to qualify for a bonus, especially those not actively monitoring their progress.

“Practices should try to get good advice on how MIPS is going to affect them,” says Mark Friedberg, MD, MPP, senior physician policy researcher for the RAND Corporation. “It is a very complicated and changing payment model.”

PRIVATE Payers REFocus on outcomes

Private payers and physicians are always haggling over reimbursement rates, and 2019 will be no different. But as the market on both sides continues to consolidate, smaller practices may find it more difficult to negotiate for the rates they desire.

From an insurer standpoint, the overall pie to pay physicians, hospitals, and other providers is fixed, says Mark Dietrich, CPA, member of the National Society of Healthcare Business Consultants. “The largest portion of the pie goes to provider entities that have the greatest amount of negotiating leverage. Smaller practices get what’s left.”

Larger entities can not only negotiate better fee-for-service rates, but also more lucrative quality incentives for value-based care contracts, he adds. Physicians should expect the reimbursement challenges for small practices to continue. “Government policy is really designed to loosen the regulatory restriction on providers coming together,” says Dietrich. “The whole idea is that if they get more integrated provider groups along the continuum of care, they will get better data, better clinical options, and better outcomes.”

The result is that larger practices or those affiliated with health systems can extract significantly higher rates than small, independent practices, according to Dietrich. “It’s all about who has the biggest piece of the pie,” he says. “Like on the savanna, the big lion gets the most and the hyena gets what’s left.”

Small practices can help themselves in negotiations by having strong data that proves they are improving outcomes for patients, as ultimately, this lowers a payer’s costs. Experts agree that practices can expect to see more demands for data from CMS and private payers as the march to value-based care continues.

“Carriers are doing deals that generally reward physicians in value-based contracts, but minimize reimbursement increases if they are not involved in value-based benefits,” says Ken Goulet, former executive vice president of Anthem Inc. and current board member at OODA Health, which focuses on streamlining interactions between payers and providers. While he says fee-for-service won’t be completely eliminated, doctors can expect to see diminishing reimbursements in 2019 and in the future.
“Fee-for-service is going to last for a while, but it’s becoming less preferred by carriers,” says Goulet. “In 15 years, it will probably still be here, but there will be significantly higher levels of contracts in value-based care. Anyone still doing fee-for-service will find reimbursement not increasing much, so it will be less and less beneficial to be in those contracts.”

The challenge for primary care providers is that every payer has its own version of what value-based care looks like, with different measures for evaluating quality, outcomes, interaction with other physicians treating the same patient, and efficiency, says Goulet, adding that one model insurers favor is the Patient-Centered Medical Home (PCMH).

“It’s fair to say that a primary care physician or primary care practice can increase earnings by 25% in bonus payments if actively engaged in PCMH,” says Goulet. “It allows them to increase quality, improve outcomes, and lower costs, therefore triggering bonus payments.”

The appeal to insurers is to identify patients with chronic conditions and pull them back into primary care practices, which can help them manage their conditions, says Goulet, who notes that it’s not uncommon for insurers to have patients who visit the emergency department 35 or more times a year. The PCMH model was put in place not only to drive better outcomes, but provide smaller primary care practices a way to thrive in a value-based care market, so he says to expect continued emphasis on this and similar business models.

While government policy may encourage provider consolidation, private payers don’t necessarily favor it, especially if small practices can work with them to improve outcomes, “Payers do prefer independent practices, and feel that working with them can keep costs down,” says Goulet.

Reimbursement in 2019 and beyond will require an increasing reliance on data from primary care practices proving to payers that they are meeting performance measures. “Reimbursement models will become more complex and also involve more and more measures,” says Friedberg.

**Physician Fee Schedule & E/M Changes**

CMS created quite a stir in 2018 when it proposed consolidating E/M levels 2 through 5 into one payment rate. After listening to concerns from medical associations and others, the merging of payment levels has been delayed to 2021, and as currently proposed, will collapse levels 2-4 into a single payment rate, while retaining level 5 as a separate rate.

“If equating a level 2 visit with a level 5, it could create a disparity in reimbursement for those with multiple chronic conditions,” says Gilberg. Part of the reason behind the delay was the short timeline between the final rule announcement and when it would have to be implemented.

“It would be nearly impossible for all the software systems and EHR and payment vendors to get this up and running,” says Gilberg.

So for now, E/M reimbursement levels remain unchanged, but expect to see further debate on what collapsing levels 2-4 would mean to physicians, says Gilberg.

Another significant PFS change for this year is the addition of codes for virtual check-ins, allowing physicians to bill for some evaluations done over the internet or phone. “It’s a

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How telemedicine expansion will affect physician practices

KAYT SUKEL | Medical Economics

Last year may well go down as the year of telemedicine expansion.

Telemedicine, or healthcare facilitated by means of video, phone, or other telecommunications technology, has been around for decades.

Yet major players across the healthcare industry made significant investments in 2018. Pharmacy giant CVS introduced virtual care offerings to its MinuteClinics. The Cleveland Clinic announced that telemedicine would be a major component of future care across the health system. And telemedicine vendor TelaDoc announced a new global initiative supporting remote care in more than 20 languages. And those are only a few of the telemedicine-related plans announced over the past 12 months.

These initiatives beg an important question: As corporate telemedicine offerings continue to expand, what will be the impact on physicians outside of major health systems? “There is currently pressure on physicians to consider alternate shared services delivery models that telemedicine solutions can offer,” says Neha Sachdeva, M.S., a director at KPMG’s Healthcare & Life Sciences practice, referencing new ways provider organizations can extend their services using virtual care delivery methods. “But there is no one-size-fits-all strategy for telemedicine use.”

She argues that, with telemedicine platforms ranging from a few thousand to tens of thousands of dollars, physicians need to think beyond the cool factor of recent telemedicine advances and consider how such systems will improve patient health and solve business needs.

Understanding Corporate Expansion

Telemedicine, despite not being a new technology, remains a buzz word across the healthcare industry. And for good reason: Instead of costly and time-consuming in-person encounters, physicians can rely on video visits, smartphone photos or other means to assess, treat, and manage patients with medical problems.

Ana María López, M.D., FACP, president of the American College of Physicians, says that a renewed focus on value-based care has brought telemedicine into the spotlight.

“Telemedicine offers opportunities for significant savings. There is a strong case to be made for its use to expand patient access to care and to reduce medical costs,” she says. “So it’s not surprising that we are seeing more solutions out there.”

Sachdeva agrees. “There are a lot of pressures, certainly, to adopt this kind of solution,” she says. “But there are also internal drivers—to reduce wait times to see a particular provider, to offer patients, who are looking for more consumer-centric healthcare, more options about how to receive care, and to help streamline workflows for the providers themselves.”

William Morris, M.D., MBA, Cleveland Clinic’s associate chief information officer, says its foray into telemedicine is due to a combination of all of those factors.

“First, it’s the right thing for patients, when appropriate, to see them where they are and create a high-touch experience at their convenience,” he says. “But telemedicine also offers a lot of operational efficiency.”

Dr. Morris argues that when physicians can answer questions and review tests remotely, it is more efficient for the provider, the practice, and the patient. “We’re trying to change the way we think about practice—because there’s not just one way to provide care. You should be able to get our clinical expertise without having to deal with our parking,” he says.

Daniel Barchi, M.S., chief information officer at New York-Presbyterian Hospital, believes that telemedicine is poised to fundamentally change the way medical care is provided—in practices of all shapes and sizes. New York-Presbyterian currently uses telemedicine for emergency department triage as well as for peer-to-peer physician communication—and Barchi says the hospital plans to expand its offerings.

“If we are not investing in this area and providing great care and service to our patients through it, we are not going to be prepared for the way medicine is delivered in the future,” he says.

Factors to Consider

But despite these motivations, as well as multiple studies suggesting that telemedicine provide outcomes equivalent to traditional in-person visits, some physicians remain skeptical about how the technology can benefit their practices.

A recent Healthcare Information and Management Systems Society analytics survey reveals that 55% of hospital respondents were not sure they would invest in telemedicine in the next two years. A 2017 Medical Economics survey...
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To find out more about attending the induction ceremony in Washington DC, February 28, 2019 or sponsorship opportunities visit www.dermhalloffame.org
It’s a time where we can really reimagine the way we want to experience healthcare, as patients and as providers.”

William Morris, M.D., MBA, associate chief information officer, Cleveland Clinic

Telemedicine poised to change medical care delivery

Sachdeva says creating successful remote offerings won’t be as simple as following in the exact footsteps of bigger organizations but smaller providers can learn what to do, and perhaps more importantly, what not to do. It’s important for finding the right telemedicine vendor, she says—one who can work with the practice to set up a system that meets its specific needs.

77% of consumers would be more likely to select medical providers that offer telemedicine services.

“It really all goes back to, ‘Why am I doing this? What case studies makes the most sense here? Who am I trying to target? How will it help improve care and lower costs?’” says Sachdeva.

Providers who take the time upfront to answer those questions—and look closely at the factors that are driving them to consider telemedicine—will be at an advantage. They can then look to other healthcare organizations with similar drivers, or vendor partners who specialize in those areas, to help them find the way forward.

But it’s important, Barchi adds, that such analyses should be physician-led. “Where we’ve been most successful is letting our physicians tell us what issues they are facing and how telemedicine might help them better manage those issues—whether it’s reducing wait times in the emergency room or having an expert assist you on a complex surgery from 1,500 miles away,” says Barchi.

MOVING FORWARD

What can physicians outside large health systems do to counter corporate telemedicine expansion? To start: their homework. That means investigating where, when, and how remote care delivery models can help them treat patients, and the specific business cases practices hope to address through their use, Sachdeva says.

But it continues with knowing how telemedicine will link up with electronic health record (EHR) systems.

“Think about what kind of telemedicine solution you might use and what kind of documentation needs to be [in the EHR] to support the care delivery you’re providing—and your reimbursements,” she says.

Sachdeva adds that physicians need to consider medical liability when adding telemedicine services. A practice’s malpractice insurance plan may need to change to cover remote care delivery. While many physicians may assume telemedicine will raise liability, that is not always the case. Doctors should discuss their options with their insurance provider, including what type of coverage makes the most sense for the platform they are implementing.

Product liability is a concern: if the technology isn’t reliable, care can and will suffer. And practices need to review their insurance contracts, Sachdeva says. Telemedicine reimbursements can vary greatly from payer to payer—and providers may have to renegotiate some terms if they take on a telemedicine care model. “There are lots of pieces and parts to think about before deploying a system,” Sachdeva says.

Morris agrees. “I think any successful telemedicine program starts with a physician evangelist who uses facts and data to bring others along. Telemedicine isn’t something that can be done to physicians. It needs to be done with physicians,” he says.

He adds that practices need to carefully consider payment parity, or how much a physician is paid for services rendered in person versus remotely, when discussing any telemedicine deployment.
Taking place February 7-10, 2019 at the Loews Hotel, our 17th Annual South Beach Symposium will feature an increasingly dynamic agenda, rooted in the most current research in clinical dermatology & aesthetics, and focused on interpersonal attendee engagement. With a faculty team committed to implementing the newest, most innovative technologies, the event is dedicated to providing hands-on clinical applications that can immediately be integrated into practice. With a series of Specialty Sessions including Masters of Pediatric Dermatology, Superficial Radiation Therapy, and Practice Management Symposium, additional lectures will highlight the most recently emerging practices & protocols in Advances in Hair Restoration and Anti-Aging & The Dermatologist.

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Reimbursement changes are coming, but don’t forget existing opportunities

Physicians in the MIPS program must track and submit data on a dizzying array of measures, and many private payer contracts have similar metrics that require data as the proof point. If a practice does not have the data to prove patients are achieving desired outcomes, reimbursement can take a substantial hit—up to 9% from MIPS alone by 2022. Combine this with private payer contracts that continue to incentivize value-based outcomes, and a substantial part of practice reimbursement could be endangered by a lack of performance data, experts say.

Accumulating and analyzing this data can be expensive, notes Ken Goulet, former president of Anthem Inc. and current board member at OODA Health. Consequently, Goulet says, doctors can expect to see more companies helping independent practices navigate the changing reimbursement landscape for negotiation and technology-support purposes, and insurers investing more in helping practices acquire and evaluate their data.

Goulet adds that another change practices may see as early as this year is more customized arrangements for primary care, based on region or even ZIP code. “Carriers are all going to move to cloud-based capability and moving away from significant legacy software systems to pay claims,” he says. Once implemented, these systems will allow for flexibility in value-based contracts, faster payments, and easier interaction between providers and insurers.

Telemedicine poised to change medical care delivery

“You need to align incentives—for the patient and the physician,” he says. “But you also need to think about reimbursement. It’s important that any telemedicine solution reflects the work of the physician.”

He maintains that just because doctors are seeing patients virtually does not mean less work is involved than an in-person visit. “These visits still take time and are still leveraging a physician’s intellectual capital in terms of practice and expertise,” he notes.

Telemedicine’s impact on medical practices

Telemedicine holds a lot of promise to help medical practices promote efficiency, reduce costs, and increase patient satisfaction. But Lopez cautions that it is just another tool in a clinician’s care delivery toolbox, not a health-care panacea.

“As with any tool used for care to patients, it’s important to use it appropriately,” she says. “It’s important for physicians to take a long view, assess where it can appropriately answer the diagnostic questions at hand, and make sure they are doing the right clinical thing for each and every patient.”

Morris says that telemedicine scales well—from large health systems like Cleveland Clinic to smaller rural practices. By taking the time to plan, looking at everything from the financials to changes in practice workflows, even smaller practices can reap the benefits.

But consumer expectations will drive even the smallest providers to find ways to affiliate with organizations who can help them implement at least some telemedicine options. With the technology continuing to expand across the globe, patients will increasingly expect access via telemedicine.

“Instead of calling a pager or service, the patient is going to expect a quick video visit. I think we’ll see adoption being less physician-driven and more consumer-driven as time goes on,” he says.

Morris cautions that no two practices are the same—and there are a multitude of experiences that telemedicine may augment at the provider level.

“Telemedicine can help with many different cases in a way that benefit the patient, the provider, and the financial systems without the burden of overhead involved with an in-person visit,” says Morris. “It’s a time where we can really reimagine the way we want to experience healthcare, as patients and as providers.”
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Cybersecurity and medical devices: What to know

RACHEL V. ROSE, J.D., MBA | Medical Economics

The Food and Drug Administration (FDA) has drafted new guidance related to medical device cybersecurity and the relationship with HIPAA.

Building on previous writings from 2014, the FDA issued an updated draft guidance Oct. 18, 2018, entitled Content of Premarket Submissions for Management of Cybersecurity in Medical Devices – Draft Guidance for Industry and Food and Drug Administration Staff.

The guidance defines cybersecurity as “the process of preventing unauthorized access, modification, misuse or denial of use, or the unauthorized use of information that is stored, accessed, or transferred from a medical device to an external recipient.” Translated into “HIPAA language,” this requires the availability and integrity of the device—and its data—remain intact.

The broad scope of the guidance encompasses FDA medical device premarket submissions for effective cybersecurity risk management, continued cybersecurity management to reduce the risk of physical harm to patients, and satisfying HIPAA requirements.

While not binding at the moment, the guidance is important because it references laws that are in effect. The guidance incorporates HIPAA’s Privacy Rule, Security Rule, and Breach Notification Rule as well as the Federal Food, Drug, and Cosmetic Act (and related laws, e.g., the Medical Device Amendments of 1976) for branding and labeling provisions.

The guidance identifies two types of devices, Tier 1 and Tier 2. Tier 1 devices are said to carry a higher cybersecurity risk and have two associated criteria:

1. capable of connecting (e.g., wired or wirelessly) to another medical or non-medical product, a network, or the Internet and
2. a cybersecurity incident affecting the device that could result in patient harm to multiple patients.

Tier 1 devices include pacemakers, brain stimulators, and nerve stimulators. The guidance makes sense given the parts of the body that are affected by the devices.

By way of contrast, a Tier 2 device is “[a] medical device for which the criteria for a Tier 1 device are not met.” This includes an electronic device that creates, receives, maintains, or transmits protected health information (PHI) or is used in medical treatment but does not impact a body part vital to life.

The guidance recommends complying with the National Institute of Standards and Technology (NIST) and the Federal Information Processing Standards (FIPS). This should not come as a surprise for two reasons. First, the government is required to use these standards internally. Second, both NIST and FIPS are expressly stated in a variety of laws and regulations, including the HIPAA Final Omnibus Rule.

There is a specific section in the guidance entitled Maintain Confidentiality of the Data. The FDA intertwines HIPAA and the obligations between a covered entity and a business associate as well as maintaining data confidentiality. In this context, confidentiality falls under the HIPAA umbrella.

For the purposes of this guidance, other harms such as loss of confidential PHI are not considered patient harms. Although protecting the confidentiality of PHI is beyond the scope of this document, it should be noted that manufacturers and/or other entities, depending on the facts and circumstances, may be obligated to protect the confidentiality, integrity, and availability of PHI throughout the product lifecycle in accordance with applicable federal and state laws, including HIPAA.

Therefore, while physicians may not be involved with the cybersecurity of the device, they are still obligated to comply with HIPAA and the HITECH Act. Standards such as HIPAA Authorizations that give patients both notice and the right to opt out of having their PHI sold to a pharmaceutical company or medical device manufacturer, a comprehensive annual Risk Assessment, and a Business Associate Agreement are all required. Physicians should do their due diligence on companies in relation to those entities’ compliance with the FDA, HIPAA, and the HITECH Act.

Disclosures: Rachel V. Rose, JD, MBA, advises clients on compliance and transactions in healthcare, cybersecurity, corporate and securities law, while representing plaintiffs in False Claims Act and Dodd-Frank whistleblower cases. She also teaches bioethics at Baylor College of Medicine in Houston. Rachel can be reached through her website, www.rvrose.com.
Dr. Brian Biesman and Dr. Michael Gold invite you to the 2019 Music City SCALE Meeting. The meeting is for all physicians and clinicians interested in enhancing their practice and learning more about the latest procedures in aesthetic medicine. In addition to the educational sessions, there are live patient workshops and an exhibit hall with the leading members of the industry.

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When she goes into a practice for an evaluation, she approaches the task much like a physician, “doing a complete history and physical.” She initiates the process by inviting staff to weigh in, a move that would likely gain Deming’s approval.

“He said changes should happen from the ground up and not the top down,” she says. “People doing their jobs every day know what else needs to be done—and changed. I encourage the physician and manager to really listen to staff, who will know ideas will be welcomed instead of shot down.”

Get creative. Consider holding contests for the “best idea,” with prizes like credit-card-acquired airline miles or a gift certificate—or maybe even time off.

**THINK POSITIVE**

“As a leader, and as a ‘salesperson,’ you don’t want to be negative,” Phairas says. “Instead, think of being persuasive, confident, and upbeat about supporting the need for change and the benefits it will bring.”

Talk openly about what staff imagines is the worst that can happen, or about other objections, she says. Then you ask questions like:

- “Who’s going to be willing to try this?”
- “What are you doing that you think is redundant?”
- “Why are you still doing it?”

The reply to the last question is often “because it’s the way we’ve always done it.” Phairas suggests a follow-up of, “What do you think might be more efficient and better for doctors, staff and patients?”

Historically, a third of participants will be early adopters, a third will be naysayers and the remaining third will sit squarely in the middle, she says.

“It’s important to tell the early adopters, ‘I’m so pleased you’re willing to try,’ and I’m optimistic that others will come along with you,” says Phairas. “Celebrate the old, yet articulate how good things will be in the future.”

Don’t be afraid to “mix it up,” and have the front desk sit with billing, for example, so both can learn how—and why—the other works as they do.

“Get them to problem-solve together on quality improvement techniques,” Phairas says. “Make a flow chart and document ‘steps we do to achieve this’ to see real progress.”

**WHAT THE SCIENCE SAYS**

“Clinical practice change is difficult.” So begins the background explanation of a small 2017 study in Implementation Science, for which endocrinologist David C. Aron, M.D., was a co-author. Dr. Aron is a research professor at Cleveland VA Medical Center and Case Western Reserve University.

“This is illustrated by the proverbial 17-year time lag from idea to practice and the lag in evidence use in practice,” the study reports.

The study cites physicians’ “difficult time” adopting new practices, and having even more trouble “unlearning” outmoded ones. It also notes “sparse literature” on the unlearning part.

The authors acknowledge that physicians face various struggles in order to successfully change practice and restore the “equilibrium.” They also conclude that this struggle involves evidence itself and tensions between evidence and context.

“This process occurs in the context of the whole system in which physicians practice,” they say.

**REMEMBER WHY YOU CHANGE**

We all know change isn’t easy, but “it takes a conscious effort and mindfulness—along with collaboration,” says Dr. Aron. “Most important, it takes focusing on the patient.”

Meanwhile, don’t forget to be kind to yourself.

“When physicians look inside and think about changes in their practice, they may ask themselves, ‘What was I doing before? Was I actually hurting someone?’” he says.

“You were doing the best you could with the information you had available,” Dr. Aron says. “During my 40-year career, the pendulum has swung for many things we do in medicine, more than once, good then bad, then good again.”

The authors conclude that clinical practice is in a constant state of change—which is multidirectional—with unlearning and learning being “punctuation” marks in the spectrum.

So go forward and make change so you don’t miss a thing. Do so with this John F. Kennedy quote in mind, says Phairas. “Change is the law of life. And those who look only to the past or present are certain to miss the future.”

**Reference**


Change isn’t easy, it takes a conscious effort and mindfulness—along with collaboration. Most important, it takes focusing on the patient.”

David C. Aron, M.D., research professor, Cleveland VA Medical Center and Case Western Reserve University
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CeraVe hyaluronic acid serum available nationwide

CeraVe has expanded its portfolio with a new HYDRATING HYALURONIC ACID SERUM. Developed with dermatologists, the product aims to nourish stressed, dulled and dehydrated skin with hyaluronic acid and vitamin B5.

Like other CeraVe products, the serum also features Multivesicular Emulsion (MVE) technology, which keeps the key ingredients inside to increase delivery and optimal absorption. The product can be used alone or with a moisturizer. Its paraben- and fragrance-free, gel-cream formula is lightweight and helps to heal and support the skin's natural barrier.

The serum is available at drugstores throughout the United States.

FOR MORE INFORMATION: cerave.com

HydraFacial announces new product line

The HydraFacial Company recently introduced its new, daily 3-step regimen HYDRAFACIAL ESSENTIALS. The skincare line is designed to complement the HydraFacial treatment patients receive in the office.

Cleanse Cleanse: Safe for all skin types, this product gently cleanses without striping the skin of its natural oils, according to the company.

Protect SPF 40 Day Cream: This multipurpose cream contains titanium and zinc oxide. It moisturizes and protects the skin from both pollution and UVA, UVB and HEV rays, says the company. The product comes in a universal tint and an untinted version.

Restore Night Cream: Gentle on the skin, this product contains Myristoyl Nonapeptide-3, and antioxidant and peptide complexes. It helps increase cellular turnover to give skin a brighter, younger appearance.

This line is available in select spas and physician offices where HydraFacial treatments are performed.

FOR MORE INFORMATION: hydrafacial.com

At-home therapy provides drug-free treatment for psoriasis

Luma Therapeutics has launched ILLUMINATE SYSTEM, an FDA-cleared at-home treatment for plaque psoriasis. The light-based therapy was inspired by the Goethean regimen, a treatment that dates back to the 1920s.

Developed in partnership with the Mayo Clinic, Illuminates features patented hydrogen with cool far micro-globules and a narrowband UV LED light system, which work together to moisturize skin, decreases inflammation and suppresses overactive immune cells. The product is controlled by a smartphone app and a proprietary app-based dosing algorithm.

In the third clinical trial for Illuminates, 92% of 26 patients experienced meaningful clearance at 6 weeks, and patients continued to see improvements even after completing the six week treatment.

Patients can use Illuminates on to 4 areas at once, and are directed to use the therapy every day for six weeks.

FOR MORE INFORMATION: illuminates.com

FDA approves Ortho Dermatologics’ new psoriasis topical

Ortho Dermatologics has begun distribution BRYHALI™ LOTION, 0.01% to U.S. wholesale pharmaceutical distributors. The topical is a new agent to superpotent corticosteroid recently approved by the FDA for the treatment of plaque psoriasis in adults for up to eight weeks.

In two clinical trials, patients applied BRYHALI Lotion once daily for eight weeks. The topical was shown to be relatively well-tolerated with no increase in epidermal atrophy. In Study 1 and Study 2, 37 percent and 38 percent of patients, respectively, achieved success of eight weeks compared to eight percent and 12 percent of patients treated with vehicle. The most common adverse reactions were respiratory tract infection, application site dermatitis and hyperglycemia.

“Topical steroids are the most frequently used treatment for psoriasis, but come with increased risk of adverse events and a duration of use limited to two to four weeks. With BRYHALI Lotion, I’m excited to offer my patients a topical steroid option that can be used for up to eight weeks without sacrificing tolerability, and with proven efficacy,” says Lawrence J. Greer, M.D., a lead investigator on the BRYHALI Lotion Phase 3 studies and associate clinical professor of Dermatology at George Washington University School of Medicine in Washington, D.C.

FOR MORE INFORMATION: ortho-dermatologics.com
In January, three physicians led by Douglas Grossman, M.D., Ph.D., of the Huntsman Cancer Institute, University of Utah Health Sciences Center, Salt Lake City, published an article in the *Journal of the American Academy of Dermatology* that addresses controversial issues associated with the staging, treatment and surveillance of early-stage melanoma. Dr. Grossman, with Marki Klapperich, M.D., (University of Wisconsin-Madison) and Glen M. Bowen, M.D., (University of Utah Health Sciences Center), reviewed the new data to provide an up-to-date analysis that addresses issues for which there are little-to-no guidelines. In this table, we highlight frequently asked questions.

### EARLY-STAGE MELANOMA

#### Surveillance

| Year | Chances of Recurrence
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<tbody>
<tr>
<td>1</td>
<td>0.99%</td>
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<tr>
<td>5</td>
<td>2.06%</td>
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<tr>
<td>10</td>
<td>3.17%</td>
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<td>20</td>
<td>5.34%</td>
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#### How often should patients who have had early-stage melanoma undergo skin examinations?

- This should depend on the patient’s risk of recurrence, but consider your patient's unique case. This may influence how often skin examinations should be performed.

#### How often should skin examinations be conducted according to the NCCN?

- The NCCN recommends skin exams every 6-12 months for five years after an early-stage melanoma diagnosis and then, annually for life.

#### In practice, what is the norm among physicians for skin check frequency?

- For patients who are within five years of a melanoma diagnosis, most physicians (63% according to one survey) prefer annual exams after five years; 49% of physicians prefer follow-ups at six months within five years of a melanoma diagnosis.

#### What if your patient has had multiple primary melanomas or a family history of melanoma before the age of 40?

- The overall risk of developing subsequent melanomas is higher in these cases, so more frequent screenings may be best especially for patients with complex cases, such as those with numerous atypical nevi. These can be monitored by photography or digital dermoscopy.

#### What if my patient regularly conducts self exams at home? Should that determine how often in-clinic exams are conducted?

- Research shows that self exams can be effective for identifying recurrence or problem areas, but not all patients adhere to regular skin checks. For this reason, skin exams by a dermatologist are recommended.

#### My patient insists on routine imaging. Is that necessary?

- Routine imaging of patients with low-risk localized melanoma (stages 0-IIA) is not necessary at either diagnosis or follow-up. And, routine imaging to screen for asymptomatic recurrence beyond three to five years is not recommended.

- Routine imaging of stage IIC patients is most beneficial during the first four years of the diagnosis.

- For patients with stage IIB and IIC disease, NCCN guidelines recommend physical examination every six months and regional ultrasound scans in the first few years of a diagnosis.

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CHALLENGES IN THE MANAGEMENT OF MODERATE-TO-SEVERE Adult Atopic Dermatitis
PANELISTS

Norman Levine, MD, is a practicing dermatologist in Tucson, AZ. He graduated from the University of Michigan Medical School before completing his residency in dermatology at Albert Einstein College of Medicine in New York. He has been in private practice for 12 years after a 28-year career in academic dermatology at the University of Arizona.

Elaine Siegfried, MD, has been a practicing pediatric dermatologist since completing her residency training in pediatrics and dermatology in 1991. She is currently professor of pediatrics and dermatology at Saint Louis University School of Medicine and director of pediatric dermatology at SSM Health Cardinal Glennon Children’s Hospital in St. Louis, MO. The focus of her clinical practice is children with congenital and acquired skin and skin-related conditions. She has published more than 100 peer-reviewed articles and is an editor of The Textbook of Pediatric Dermatology. She has also served as principal investigator for multiple clinical trials in atopic dermatitis, psoriasis, acne, and other dermatology-specific disorders.

Matt Zirwas, MD, is a nationally recognized expert in eczema, psoriasis, and contact dermatitis who practices at Bexley Dermatology in Bexley, OH. He has published more than 150 peer-reviewed articles and is an author of the 7th Edition of Fisher’s Contact Dermatitis. His specific interests include adult atopic dermatitis, pruritus and urticaria, allergic and irritant contact dermatitis, rosacea, nonscarring alopecia, and psychodermatology.

Peter Lio, MD, is a clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine in Chicago, IL. He received his medical degree from Harvard Medical School and completed his internship in pediatrics at Boston Children’s Hospital and his dermatology training at Harvard where he served as chief resident in dermatology. Dr. Lio is the founding director of the Chicago Integrative Eczema Center and currently serves as a board member and scientific advisory committee member for the National Eczema Association. He has authored more than 100 publications and contributed to the publication of two textbooks.

Melissa Knuckles, MD, is a dermatologist in Corbin, KY. She completed her internship at Vanderbilt Medical Center and dermatology residency at the University of Louisville and St. John’s Institute of Dermatology through Guys, King’s College, and St. Thomas hospitals in London, United Kingdom. Her practice focuses on the treatment of adult and pediatric psoriasis, atopic dermatitis, carcinomas of the skin, acne, and urticaria. She has actively participated in clinical trials focused on psoriasis, atopic dermatitis, and acne rosacea, as well as several psoriasis studies/registries.

COMMERCIAL SUPPORT

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**EVALUATING THE PATIENT WITH NEWLY DIAGNOSED AD**

**DERMATOLOGY TIMES:** When you are seeing an adult patient with potential AD for the first time, what are the most important components of that initial evaluation?

**Norman Levine, MD:** AD is a clinical diagnosis, so the physical exam matters tremendously. Once I have been able to establish that the patient has eczema, there is really nothing more that needs to be done to make the diagnosis.

From there, it’s a matter of establishing a care plan based on several factors. One is the degree of disease severity. A second is the degree to which a patient is interested in addressing their symptoms. A third involves financial issues because insurance coverage often dictates what we can offer patients.

**Elaine Siegfried, MD:** My practice is exclusively pediatric. In that population, age of onset is an important diagnostic consideration. The great majority of cases of AD begin before age 5 years and most before age 2 years. It’s also important during an initial visit to find out what, if any, prior treatments the patient has tried and understand which have and have not had any impact.

**Peter Lio, MD:** In my new adult patients, if they tell me they have had eczema since childhood, that’s a pretty clear sign that true AD is the appropriate diagnosis. But if they tell me it’s a new-onset rash, this gets me worried about a couple of other possibilities, in particular allergic contact dermatitis. In those patients, I will perform a comprehensive patch test. If something looks unusual or test results are inconclusive, I may also consider a skin biopsy. In the majority of these patients, the diagnosis will indeed turn out to be AD, but a little blip in test results does make me concerned that something else may be going on.

**Matt Zirwas, MD:** Up until 2 years ago, I classified patients who primarily had spongiotic dermatitis on biopsy, negative patch testing, and onset of eczema later in life as having dermatitis unspecific (ie, dermatitis NOS [not otherwise specified]). The spongiotic biopsy confirmed it was dermatitis, but because they did not have childhood onset of eczema, it wasn’t classic AD, and the negative patch testing ruled out contact dermatitis, leaving no definitive cause of the dermatitis.

So even though a patient might in fact have met the Hanifin and Rajka criteria for the diagnosis of AD (Table 1), because the systemic treatments for dermatitis NOS and AD in adults were the same (ie, systemic steroids, cyclosporine, methotrexate, azathioprine, mycophenolate, phototherapy), formally diagnosing them with AD would not have affected how I treated them. Since the FDA’s approval of dupilumab, however, a formal diagnosis of AD absolutely matters because it determines if they are a candidate for that drug. As a result, I started applying the Hanifin and Rajka criteria to determine if a patient was a candidate for dupilumab, and it turns out that approximately 90% of my adult patients with dermatitis NOS do meet the Hanifin and Rajka criteria for AD, even though they didn’t have childhood-onset eczema.

**DERMATOLOGY TIMES:** What are some of the more common and challenging side effects of AD for a dermatologist to manage?

**Melissa Knuckles, MD:** The most common side effects include anxiety, depression, pruritis, ocular changes, and really just dealing with the burden of the disease. Because of the psychological and emotional impact of AD, the most important thing for dermatologists is to give our patients hope when they come into our office. Hope is a big thing for these people—so many of them have been everywhere trying to get relief before we see them.
Dr. Lio: I’m fortunate to work in a center that has an integrative, multidisciplinary approach to the care of AD. One of the things I have found to be unusually helpful is the presence of a hypnotherapist. It’s amazing. At our monthly group meetings, the hypnotherapist is such a beloved presence because she gives a great lecture about how stress, anxiety, and depression all play a part in the vicious cycle of AD.

I will definitely say that particularly for patients who feel there is a big stress or an anxiety component to their condition, cognitive behavioral therapy and similar approaches that include modalities such as hypnotherapy and relaxation can really be effective in helping them overcome some of those barriers.

Getting patients to buy into these types of sessions is not always easy. It’s important they understand that our recommendation for additional professional help is not because we think they are crazy or psychologically damaged, but because of the significant disease burden of AD and the stress it can put on patients. One of my favorite strategies is to zero in on sleep issues. We know that sleep problems alone are bad for mental health. So, I don’t care if patients turn to sessions of tai chi, meditation, acupuncture, or something else. What our patients need is that push to help them find peace in their lives.

Dr. Zirwas: In other words, make sure they understand we are saying that the eczema is causing psychological problems, not that psychological problems are causing the eczema.

Dr. Siegfried: It certainly can be difficult teasing out which of our patients with AD have psychiatric comorbidities and then helping them access professional mental care. A link between AD and attention deficit disorder, as well as anxiety and depression, has been well-established. It is not uncommon for AD to negatively impact school performance and attendance. A small handful of my patients have suffered from severe depression and even suicidal ideation requiring hospitalization. In a few, these psychiatric morbidities profoundly improved with the use of dupilumab. It’s been amazing to see that.

Dr. Zirwas: I have a story along those lines about a patient of mine with severe eczema who was part of a same-sex couple. They always came in for visits together. My patient always came across as sort of an odd person while his partner was a really interesting, cool person. I could never understand what the two of them were doing together. I couldn’t figure out what the partner saw in my patient that made him want to be with him.

Well, we got my patient’s eczema better and their personalities totally switched. Everything about my patient was different once his eczema cleared up and he started sleeping without sedatives. Now, he was the

### TABLE 1  HANIFIN AND RAJKA CRITERIA FOR THE DIAGNOSIS OF AD

<table>
<thead>
<tr>
<th>MAJOR CRITERIA (must have at least 3)</th>
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<tbody>
<tr>
<td>Pruritus</td>
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<tr>
<td>Dermatitis affecting flexural surfaces in adults and the face and extensors in infants</td>
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<tr>
<td>Chronic or relapsing dermatitis</td>
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<tr>
<td>Personal or family history of cutaneous or respiratory atopy</td>
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<table>
<thead>
<tr>
<th>MINOR CRITERIA (must have at least 3)</th>
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<tbody>
<tr>
<td>Xerosis</td>
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<tr>
<td>Ichthyosis/palmar hyperlinearity, keratosis pilaris</td>
</tr>
<tr>
<td>Immediate (type 1) skin test reaction</td>
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<tr>
<td>Elevated serum IgE</td>
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<tr>
<td>Early age of onset</td>
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<tr>
<td>Tendency toward cutaneous infections (especially Staphylococcus aureus and herpes simplex), impaired cell-mediated immunity</td>
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<tr>
<td>Tendency toward nonspecific hand or foot dermatitis</td>
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<tr>
<td>Nipple eczema</td>
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<tr>
<td>Cheilitis</td>
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<tr>
<td>Recurrent conjunctivitis</td>
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<tr>
<td>Dennie-Morgan infraorbital fold</td>
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<tr>
<td>Keratoconus</td>
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<tr>
<td>Anterior subcapsular cataracts</td>
</tr>
<tr>
<td>Orbital darkening</td>
</tr>
<tr>
<td>Facial pallor, facial erythema</td>
</tr>
<tr>
<td>Pityriasis alba</td>
</tr>
<tr>
<td>Anterior neck folds</td>
</tr>
<tr>
<td>Itch when sweating</td>
</tr>
<tr>
<td>Intolerance to wool and lipid solvents</td>
</tr>
<tr>
<td>Perifollicular accentuation</td>
</tr>
<tr>
<td>Food intolerance</td>
</tr>
<tr>
<td>Course influenced by environmental and emotional factors</td>
</tr>
<tr>
<td>White dermographism, delayed blanch</td>
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Source: Hanifin JM, Rajka G.2
more interesting person and I wondered what he saw in his partner. That just shows the dramatic effect that eczema can have on our patients and the impact we can make on them well beyond their visible skin issues.

**SETTING APPROPRIATE TREATMENT GOALS IN PATIENTS WITH AD**

**DERMATOLOGY TIMES:** Let’s talk about setting goals for your patients with moderate-to-severe AD (Table 2) and what level of improvement you tell your patients they can attain. What does that initial conversation sound like?

**Dr. Levine:** Well, I want them to get “all better.” Now what exactly does that mean? The biggest issue for me is that they are not itchy anymore. The itch is what ruins most of our patients’ lives, so whatever we can offer from a pharmacologic perspective to make their itch go away, I’m all for it. That’s the first step. And the second step is that if their itch is better, the eczema is going to get better. That’s my goal.

The first question I ask patients with AD when they come in for a return visit is: “Are you still itchy?” And the second question is: “Are you sleeping better?” If I get the answer I want to those two questions, then everyone is generally happy. If you get your patient better by whatever means, they will feel better, they will sleep better, and they will often be less depressed.

**Dr. Zirwas:** I’m struck by how much the introduction of dupilumab has changed the way I set goals for patients with AD. Before its approval, I would prescribe a lot of cyclosporine, methotrexate, and mycophenolate mofetil—and certainly I still do—but my goal when we were limited to those drugs was to get my patients 90% better. I would tell my patients: “If you are 90% better, we know we’ve got you on about the right dose of medication. I don’t want you 100% better because that means you are on too high a dose and we’ll need to lower it to reduce your risk of side effects.” These traditional systemic drugs are entirely dose dependent in regard to side effects.

Now that we have dupilumab in our arsenal, I am comfortable telling patients that our goal is to get them 100% better. That means no itch and no rash. It also means no systemic steroids. There was a study in 2017 showing that patients treated with a short course of systemic steroids have a 7-fold increased risk of developing sepsis.1 I always set the goal of getting patients well enough so that they will not need systemic steroids at all.

**Dr. Levine:** Let me offer a slightly different perspective. If you look at the trial data results for dupilumab—which are backed up with my personal experience, shooting for 100% improvement in patients with AD is perhaps overly optimistic. Yes, you can get patients a

<table>
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<th>TABLE 2</th>
<th>DEFINITION OF MODERATE-TO-SEVERE AD</th>
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<tr>
<td>1. Moderate-to-severe AD may be considered when 1 or more of the following features are present:</td>
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<tr>
<td>• A minimum involvement of 10% BSA</td>
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<td>• Regardless of BSA</td>
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<tr>
<td>– Individual lesions with moderate-to-severe features</td>
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<tr>
<td>– Involvement of highly visible areas or those important for function (eg, neck, face, genitals, palms, and/or soles)</td>
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<tr>
<td>• Significantly impaired QOL</td>
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<tr>
<td>2. Current disease severity scales and QOL scales, although validated for use in clinical trials, are not practical for routine utilization in clinical practice.</td>
<td></td>
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<tr>
<td>3. Although global assessment scores have not been validated in office settings, it is simple to classify disease as clear, almost clear, mild, moderate, or severe.</td>
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<tr>
<td>4. Clinicians should actively assess the impact of disease on QOL during clinic visits (i.e., sleep, pruritus, impact on activities of daily living and work).</td>
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<tr>
<td>5. No biomarkers, including serum IgE, are currently recommended for assessment of disease severity.</td>
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Abbreviations: AD, atopic dermatitis; BSA, body surface area; QOL, quality of life.
lot better, but the data show that an improvement of approximately 80% is more realistic for the majority of patients. I tell this to my patients, and the majority of them are OK with that. If they end up getting completely better, that’s great, but that is not my expectation with dupilumab.

**Dr. Zirwas:** I agree, and I should have phrased my answer differently. I tell my patients that, on average, people get 80% better on dupilumab but that my experience is approximately 20% of patients will get 100% better, 5% won’t get better at all, and the rest improve between 60% and 80%. But I do tell everyone up front that there is a chance they will get 100% better, even if that is not what I am expecting for most of them. I find that setting the bar high makes patients more motivated.

**Dr. Siegfried:** Treatment goals for children with AD are somewhat different than for adults, in part because of the lag in available data supporting pediatric safety and efficacy for new treatments, along with barriers to medication access. I emphasize the importance of recognizing and addressing likely triggers rather than unlikely contributing factors. Many parents focus on environmental exposures like pets or dietary exposures. More important contributing factors not obvious to most are skin care products, skin germs, changes in ambient humidity, psychic stress, and illness.

I spend a lot of time educating patients to overcome myths and stop counterproductive use of OTC products that contain potential contact allergens. When they start topical treatment, I always provide guidance about therapy and monitor the amount of topical medications they use.

Topical treatment can be complicated. Patients need to understand the importance of using an adequate, but not excessive, amount of topical medication. I’m also a big believer in bleach baths. For children who do not fare well on conservative treatment, I don’t hesitate to start systemic therapy.

**DERMATOLOGY TIMES:** What are some of the other common myths you need to debunk among your patients with AD?

**Dr. Knuckles:** I tell all my patients who have eczema that “You don’t paint the house when the sewers are leaking.” They think AD is solely a skin disease and that they can just slap a cream on and it will all get better. I have to explain to them that there is an internal causation to their inflammation that makes it more complicated. I also get a lot of patients who think the only places they have to worry about on their skin are where it is red. They need to be educated that it’s not just their lesional skin that has eczema, but that their unaffected skin is also inflamed.

**Dr. Zirwas:** The biggest myth I deal with is steroid phobia. Studies have shown that approximately 70% of patients have steroid phobia, meaning that in 70%, the fear of side effects is clearly out of proportion to the actual risk. I’m just talking about adults. In children, it might be a totally different balance. There are some conditions for which the treatment is potentially worse than the disease, but in AD the disease is far worse than the potentially worst things that can happen with topical treatment. I often ask patients what they are afraid of with the use of topical steroids, and most of them say “thinning of my skin.” I then ask if they would rather have thin skin or skin that is scratched and bleeding from eczema. It still usually doesn’t get through to them, though. There is just this specter of “badness” looming when topical steroids come up.

**Dr. Siegfried:** Food allergies are a big one for me. The great majority of people who believe they have food allergies do not react to placebo-controlled food challenges. However, many who have modified their diet for years develop an intrinsic fear of liberalizing their food intake. That is an unintended, potentially crippling consequence.

**Dr. Lio:** When I have a patient who won’t stop focusing on potential food allergies and continues to ask about more tests and questions like “Should I switch to a gluten-free diet?” long past the point of potential utility, I try to turn the story around. I try to provide a more modern take.

For a long time, the narrative was that food allergies are driving the disease. But now with new data we know that we’ve had it backwards and it’s really the leaky skin, the impaired barrier, that is causing transcutaneous sensitizations to certain foods. So instead of worrying about what the patient is eating, our priority needs to be getting their skin under control, with the idea that a better skin barrier could potentially decrease the development of future allergies, at least theoretically.
Relaying the story in that fashion can be very impactful. I often see the lightbulb go on in my patients’ heads and they tell me: “You know, that makes a lot of sense.”

Dr. Siegfried: A favorite sound bite of mine for patients who are convinced that food allergy is the cause of their eczema is: “Food allergies are more common in people who have eczema, but food allergy doesn’t cause eczema, just like asthma or allergic rhinitis doesn’t cause eczema.” While these may occur concurrently in any given patient, one does not drive the other.

Dr. Zirwas: I love how you both turn things around in such an impactful way. Just as with the psychological aspects of AD, you’re getting patients to realize that the eczema is causing the food allergies rather than the food allergies causing the eczema. That’s a great sound bite I’m definitely going to use in the future.

CONVENTIONAL TREATMENT OPTIONS IN ADULT PATIENTS WITH MODERATE-TO-SEVERE AD

DERMATOLOGY TIMES: What does your mental treatment algorithm look like for adult patients diagnosed with moderate-to-severe AD? Where do you typically start with them?

Dr. Lio: I typically begin by making sure the patient is following basic skin care procedures and avoiding obvious triggers such as the use of fragranced soaps, rubbing/scratching their skin, or wearing wool. I’ll then move on to talking about moisturizers, typically by bringing over a palette of different options that I like and letting the patient try them to find one that feels good on their skin.

Once we establish a moisturization protocol, my first line in most patients is a topical steroid for up to 2 weeks. Once there is significant improvement, if it’s a patient with only mild eczema, I’ll typically simply continue with moisturizer, but if it’s someone with a more persistent condition, I’ll typically switch them to a nonsteroidal agent such as a calcineurin inhibitor to “finish the job” and get the skin totally clear, hopefully keeping it that way.

For those patients who present with moderate-to-severe AD, I’ll try to see them about 2 weeks after they have started on the topical steroid, when I will look for three things:

1. Are they better?
2. Can I keep them clear safely without overusing potent corticosteroids?
3. Can I keep them clear sanely without the patient losing their mind by constantly needing to apply tons of ointments and being endlessly greasy and ruining their clothing?

If the answer to any of those questions is no, that’s when I consider the jump to systemic therapies. I think we are all becoming much more aggressive with our treatments these days because our patients do not need to suffer anymore. We have the tools available to get and keep them better.

I will typically turn to dupilumab or phototherapy at this stage. Phototherapy can be a good option, but it involves so many issues related to time, money, and logistics that it’s not a viable option for a lot of my patients. I used to use cyclosporine in many of my AD patients, but now I try to reserve it and only use it in those patients for whom I cannot get dupilumab or for the smaller group that does not achieve enough improvement on dupilumab alone.

Dr. Levine: My general approach is similar. For adults, I will typically start them on a topical steroid, usually triamcinolone. And of course, I have my AD patients use moisturizers. If these patients’ lives are being impacted in a significant fashion—which is often the case in adults with moderate-to-severe AD—I’m quick to move to systemic therapy if the topical steroid is not working.

I will often try to get dupilumab for these patients, but there are some significant regulatory and insurance barriers to getting that drug. If I can get it approved, that is where I’ll typically go, but if not, cyclosporine, methotrexate, and azathioprine are all options. I deal with a lot of insurance companies that require a patient fail a systemic therapy before they will approve dupilumab, and oddly enough, many also require that they fail a topical calcineurin inhibitor.

The problem with our current systemic therapies is that patients need lifelong treatment. While these
therapies can help induce remission of an AD patient’s symptoms, they do not produce a cure. Patients need to understand that once they start on something, they are going to be on it for the long haul. I try to get a sense early on from my patients whether they will have the motivation to adhere to our plan. For instance, I will not start a patient on methotrexate if I’m reasonably sure they won’t come in for the necessary blood tests.

**DERMATOLOGY TIMES:** For a patient you are considering starting on an immunosuppressant, how long will you wait for that patient to respond to topical therapy before you move to something else?

**Dr. Knuckles:** I’ll usually wait about 2 weeks. If I don’t see a response by then, I’ll switch to systemic therapy. I tend to move pretty fast.

**Dr. Levine:** I’ll usually wait a little longer, perhaps 1 month, because the next step into systemic therapies is fairly significant. I want to make sure that patients have given the simpler, less expensive, and safer medications a try before I move forward with something else.

**Dr. Siegfried:** My practice is not restricted by insurance type or ability to pay, so the demand limits my ability to follow up as soon as I would like. Although frequent follow-up definitely supports better adherence, 1 month is the best I can do and it’s usually 2 to 3 months. For children, it takes longer to recognize that they may have failed what I call “maximum conservative treatment,” a failure which is often related to adherence.

**Dr. Zirwas:** How does everyone feel about melatonin? A couple of studies have come out in favor of melatonin as improving objective measures of disease severity as well as quality of life and sleep quality in patients with AD. Combined with other recent studies that have shown anticholinergics such as hydroxyzine and doxepin effectively double an individual’s risk of developing Alzheimer’s disease late in life if taken for more than 3 years, I find myself recommending melatonin much more frequently, but I honestly can’t tell if it’s working in my patients with AD or not.

**Dr. Siegfried:** I have recommended melatonin as a presumably safe and readily available, inexpensive option, but I have not seen any patients who have reported that it was helpful. I have moved away from using sedating antihistamines in patients with AD. Not only is there growing literature about under-recognized neuropsychiatric risks but these are also not that effective. I recommend daily, non-sedating antihistamines for patients with dermatographism and a history suggestive of concomitant hives.

I also caution patients about the lack of efficacy and risks of montelukast for treating eczema. This drug continues to be prescribed for patients with AD but can cause behavioral side effects in a subset of children. In addition, the chewables contain aspartame, which cross-reacts with formaldehyde and can cause systemic allergic contact dermatitis in patients with formaldehyde allergy.

**DUPILUMAB FOR THE TREATMENT OF AD**

**DERMATOLOGY TIMES:** Throughout this discussion, we have touched on how you all use dupilumab in your adult patients with moderate-to-severe AD, but let’s talk about some specific issues. First, when you prescribe dupilumab, are you usually prescribing a corticosteroid along with it?

**Dr. Zirwas:** Occasionally, I will. Whenever I am starting a patient on dupilumab, I ask the patient to truthfully tell me how miserable they are. I explain that on dupilumab alone, if we’re lucky, it will be a couple of days before their itch starts getting better. If we’re not lucky, it might be 6 weeks before their itch starts getting better. Do they want relief badly enough that it’s worth taking the small risk of getting a severe infection with a short course of systemic corticosteroid? I leave the decision up to them. I’m willing to prescribe it if they really are desperate for the relief, but most patients end up opting not to go on the steroid short term whenever they start dupilumab.

**Dr. Lio:** I try as best I can to avoid using oral steroids in patients taking dupilumab. When we all first began using dupilumab, most patients were transferred over
INDICATION
DUPIXENT is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Conjunctivitis and Keratitis: Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder in these patients. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Atopic Dermatitis Patients with Comorbid Asthma: Advise patients not to adjust or stop their asthma treatments without consultation with their physicians.

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

ADVERSE REACTIONS: The most common adverse reactions (incidence >1%) in atopic dermatitis patients are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.
Consider **DUPIXENT** and

**TRIAL DESIGNS:** A total of 917 adult patients in Trials 1 and 2 (16-week trials) and 421 adult patients in Trial 3 (52-week trial) with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription treatments were randomized to DUPIXENT 300 mg Q2W or placebo. For all patients in Trial 3, lesions were treated with concomitant TCS. Eligible patients had an IGA score ≥3 (overall atopic dermatitis lesion severity scale of 0 to 4), an EASI score ≥16 on a scale of 0 to 72, and body surface area involvement of ≥10%. At baseline, 52% of subjects had an IGA score of 3 (moderate atopic dermatitis), 48% of subjects had an IGA of 4 (severe atopic dermatitis), mean EASI score was 33, and weekly averaged peak pruritus NRS was 7 on a scale of 0 to 10.¹

The primary endpoint was the change from baseline in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and ≥2-point improvement at Week 16 (38% and 36% with DUPIXENT vs 10% and 9% with placebo in Trials 1 and 2, respectively, P<0.001; 39% with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 3, P=0.0001). Other endpoints included the proportion of subjects with an IGA 0 or 1 and ≥2-point improvement from baseline at Week 52 in Trial 3 (36% with DUPIXENT + TCS vs 13% with placebo + TCS, P<0.0001), change from baseline in the proportion of subjects with EASI-75 at Week 16 (improvement of ≥75%; 51% and 44% with DUPIXENT vs 15% and 12% with placebo in Trials 1 and 2, respectively, P=0.001), and reduction in itch as defined by ≥4-point improvement in the peak pruritus NRS (51% with DUPIXENT + TCS vs 13% with placebo + TCS in Trial 3 at Week 52, P=0.0001).¹⁻⁴

EASI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment; NRS, numerical rating scale; Q2W, once every 2 weeks; TCS, topical corticosteroids.

**IMPORTANT SAFETY INFORMATION**

**DRUG INTERACTIONS:** Avoid use of live vaccines in patients treated with DUPIXENT.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
see the evidence of continuous CONTROL

Not a clinical trial patient. Images represent an EASI-75 response. See DUPIXENT clinical study responses in the full Prescribing Information. Individual patient responses may vary.

- Itch relief
- Improvement in lesion extent and severity
- Clear or almost-clear skin
- No requirement for initial lab testing or ongoing lab monitoring, according to the full Prescribing Information

IMPORTANT SAFETY INFORMATION
USE IN SPECIFIC POPULATIONS (cont’d)
• Lactation: There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Please see brief summary of full Prescribing Information on the following page.

Visit DupixentHCP.com/AtopicDermatitis to learn more

Table 1: Adverse Reactions Occurring in 21% of the DUPLEXEN Monotherapy Group or the DUPLEXEN + TCS Group in the Atopic Dermatitis Trials Through Week 16

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPLEXEN Monotherapy*</th>
<th>Placebo N=517</th>
<th>DUPLEXEN + TCS*</th>
<th>Placebo N=315</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>51 (10)</td>
<td>28 (5)</td>
<td>11 (10)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Conjunctivitis*</td>
<td>51 (10)</td>
<td>12 (2)</td>
<td>10 (9)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (1)</td>
<td>&lt;1 (1)</td>
<td>5 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
<td>3 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (1)</td>
<td>0</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection*</td>
<td>10 (2)</td>
<td>6 (1)</td>
<td>1 (1)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>&lt;1 (1)</td>
<td>0</td>
<td>2 (2)</td>
<td>&lt;1 (1)</td>
</tr>
</tbody>
</table>

*Pooled analysis of Trials 1, 2, and 4

**Analysis of Trial 3 where subjects were on background TCS therapy

†DUPLEXEN 600 mg at Week 0, followed by 300 mg every two weeks

‡Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

§Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simples.

¶Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex ulcers externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 62 (Trial 3): In the DUPLEXEN + concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPLEXEN 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPLEXEN because of the asthma (1 subject) and exfoliative dermatitis (1 subject). The safety profile of DUPLEXEN + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Asthma: A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (Asthma Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the prior year, placebo-controlled, and were administered an inhaled corticosteroid at baseline (27% female and平均age of 37 years). A total of 201 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to 2 additional controller drugs were enrolled (Asthma Trials 3). The safety profile of DUPLEXEN 200 mg Q2W + TCS group was similar to the placebo 300 mg Q2W + TCS group, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of discontinuation due to adverse events was 4% of the placebo group, 3% of the DUPLEXEN 200 mg Q2W group, and 6% of the DUPLEXEN 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPLEXEN and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 2: Adverse Reactions Occurring in 21% of the DUPLEXEN Monotherapy Group in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPLEXEN Monotherapy*</th>
<th>AS Trials 1 and 2</th>
<th>Placebo N=792</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions*</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophilia*</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Eosinophilia = blood eosinophils ≥ 2300 cells/μL, or deemed by the investigator to be an adverse event. None of the criteria for serious eosinophilic conditions [see Section 5.3 Warnings and Precautions] were met for eosinophilia.

Safety profile of DUPLEXEN through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions: Conjunctivitis: During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPLEXEN + TCS group (20 mg per 100 mg) compared with 9% of the placebo + TCS group (10 mg per 100 mg). Among asthma subjects, the frequency of conjunctivitis was similar between DUPLEXEN and placebo [see Warnings and Precautions (5.2)].

Eczema Herpeticum and Herpes Zoster: The rate of eczema herpeticum was similar in the placebo and DUPLEXEN groups in the atopic dermatitis trials. Herpes zoster was reported in <1% of the DUPLEXEN groups (≥90% of subjects per study) and in <1% of the placebo + TCS group (1% per 100 mg). In the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPLEXEN + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPLEXEN + TCS (1% per 100 mg) and of the placebo + TCS (2% per 100 mg) subjects. Among asthma subjects the frequency of herpes zoster was similar between DUPLEXEN and placebo.

Hypersensitivity Reactions: The incidence of adverse reactions reported in <1% of DUPLEXEN-treated subjects. These included urticaria, anaphylaxis, angioedema, asthma, rhinitis, nasal congestion, and allergic rhinitis [see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)].

Eosinophils: DUPLEXEN-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mL, respectively.
increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/µL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/µL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/µL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 300 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo-controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal Mls, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

Animals

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

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab, ~2% exhibited persistent ADA responses and ~4% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT, ~3% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

Antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was correlated with decreased serum dupilumab concentrations [see Clinical Pharmacology (12.3)].

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy [see Warnings and Precautions (5.1)].

7. DRUG INTERACTIONS

7.1 Live Vaccines

Antiviral use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were vaccinated with a recombinant hemagglutinin-adenovirus vectors expressing the influenza A H1N1, A H3N2, and B antigens and the pneumococcal polysaccharide vaccine (Menomune*). Antibody responses were assessed 4 weeks after vaccination. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see Clinical Considerations). In an enhanced pre- and postnatal developmental toxicity study, no adverse fetal effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 and interleukin-13 (IL-13) elicited by IL-4Rα up to 10 times the MRHD (0.3 mg/kg/day) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryotoxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

Safety and efficacy in pediatric patients (<18 years of age) with atopic dermatitis have not been established.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 250 mg (N=21) or 350 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV1 (L, mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than in adults at the respective dose level which was mainly accounted for by difference in body weight [see Clinical Pharmacology (12.3)].

The adverse event profile in adolescents was generally similar to the adults [see Adverse Reactions (6.1)].

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

Of the 197 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patient and caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharp disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions [see Warnings and Precautions (5.1)].

Concomitant Use

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see Warnings and Precautions (5.2)].

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis [see Warnings and Precautions (5.3)].

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT [see Warnings and Precautions (5.4)].

Reduction in Corticosteroid Dosage

Inform patients not to discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see Warnings and Precautions (5.5)].

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see Warnings and Precautions (5.6)].
from cyclosporine, azathioprine, or methotrexate, so that was a bridge for those people. In today’s environment, as we noted earlier, there will be a percentage of patients who won’t be helped at all by dupilumab, so those are the patients in whom I will use full-dose cyclosporine for a few weeks to cool things down.

I’ve also had a few patients who have done well on weekend-dosing cyclosporine, which has typically been used as a psoriasis treatment. A study done a few years ago showed that this sort of regimen can be effective in AD, and my experience has been largely positive as well.13 I have patients take a full dose of cyclosporine on Saturday and Sunday only along with their twice-monthly dupilumab. The cyclosporine has helped to extend the impact of the medication. There will be some patients who flare 7 to 10 days after every dose of dupilumab, so this is an option for those patients who can’t quite make it to a full 2 weeks.

I do have a few female patients in my practice for whom I have been able to successfully argue for weekly dupilumab. You can imagine, though, how difficult it was convincing their insurance companies. In a handful of others who might have seen benefit from weekly dosing, I have not been able to achieve coverage.

**Dr. Zirwas:** I tried the weekend regimen of cyclosporine in a few of my patients in the pre-dupilumab era, and it didn’t do much. I can see the logic, however, of using a regimen like that for those patients who are mostly better but are getting the breakthrough rash a few days before their next injection of dupilumab.

**DERMATOLOGY TIMES:** How do the rest of you use dupilumab in your patients with AD?

**Dr. Knuckles:** In Kentucky, it’s unfortunately mandated by all our insurance providers that AD patients need to fail at least one nonsteroidal topical medication—typically either pimecrolimus or tacrolimus—or an immunosuppressant for at least 30 days before they will approve something else. I call it the “one and done” rule. The nice part about it is that it allows me to bypass other systemic agents and go right to dupilumab.

My practice is in a semirural area and I have a lot of patients who drive several hours to see me, so it’s not often realistic to have them see me 2 weeks after their initial injection. Instead, I’ll have them call my office to tell me how they are doing.

**Dr. Levine:** I don’t typically use a bridge drug when I start a patient on dupilumab, but for those who are using a systemic agent such as cyclosporine or methotrexate already, I’ll usually keep them on it for at least a month. It can take several weeks for dupilumab to begin having an effect, but if there is improvement when the patient comes back for that initial 1-month visit, I’ll discontinue their systemic drug and continue with dupilumab into the sunset. The one thing I do tell my patients is that if they are not better after 3 months of dupilumab, we’re going to stop.

**DERMATOLOGY TIMES:** What are some of the more common and significant adverse events you have seen in patients starting dupilumab?

**Dr. Liu:** Conjunctivitis has been probably the biggest issue. It occurs in approximately 10% of patients who start dupilumab, and I’ve had to take a handful of patients off of therapy. I wrote a paper recently that focused on a case series of 12 patients with AD who developed conjunctivitis secondary to their use of dupilumab. We found that severe conjunctivitis was more likely to develop in patients with more severe baseline AD who had a good response to dupilumab and an increased atopic phenotype, so from that perspective, it is unfortunate.14

But there has been a silver lining. In each of the 4 patients in whom we had to discontinue dupilumab, their AD remained relatively improved and stable up to 18 weeks after cessation. No one regressed to baseline or had a rebound flare.14 This shows me that perhaps dupilumab does not have to be a lifelong therapy in all of our patients and that there may be hope of remission in at least some patients.

There is vicious cycling in AD. The skin barrier is broken, the immune system has gone crazy, allergens and irritants are getting in, bacterial imbalance is rampant, and behavioral aspects are practically uncontrollable. The whole thing is a mess. But perhaps if you can get it all back into a virtuous cycle, now the skin barrier heals, now the immune system calms down, now the little nerve endings to the skin regress back down, and that can become the patient’s “new normal.” Maybe it just requires maintenance dosing of cyclosporine or dupilumab every 3 months. It’s a hypothesis at this point, but something worth thinking about.

**Dr. Zirwas:** A recent patient of mine who developed conjunctivitis had a close friend who is an optometrist.
They kept trying different drops to see if anything would work while this patient stayed on dupilumab.

He ended up using lifitegrast, a drop commonly used to treat chronic dry eye. It’s a competitor to cyclosporine ophthalmic, with which we are likely more familiar. This patient had significant conjunctivitis for several months and had tried and failed several previous drops, including cyclosporine and steroid drops, but his response to lifitegrast was remarkable. His conjunctivitis basically resolved immediately.

Lifitegrast is an interesting agent. It blocks the interaction between lymphocyte function-associated antigen-1 (LFA-1) and its ligand intercellular adhesion molecule-1 (ICAM-1). It is considered safe for long-term use. My experience with it was only in this patient, so we will have to see if it is repeatable, but it’s the one example I know of a patient with dupilumab-related conjunctivitis who got better.

**Dr. Siegfried:** I’ve had the same experience with lifitegrast. It definitely needs further evaluation.

**DERMATOLOGY TIMES:** Are there any other potential side effects that you point out to your patients before they start dupilumab?

**Dr. Levine:** Injection site reactions are a possibility. You’ve got to tell patients in advance that they may have soreness for about 24 hours after an injection.4

**Dr. Lie:** I will typically mention two other concerns. Although extremely rare, it is possible to have a systemic reaction to the injection itself. I am also always sure to ask patients if they will be traveling to a place where they may be exposed to parasites before starting them on dupilumab. I had one patient who was in the midst of filling out the paperwork to start on dupilumab, and he started telling me about some upcoming work he would be doing in remote villages in Africa. I told him we would wait until he came back to start the drug. I was a little worried that if he was exposed to a parasite while abroad, his immune response to the parasite could be impaired.

**DERMATOLOGY TIMES:** What is the impact of dupilumab on patients with contact dermatitis?

**Dr. Zirwas:** My experience is that dupilumab often makes it worse. I’ve had a number of patients who were diagnosed with AD by outside dermatologists who then put them on dupilumab. When I saw these patients, their rash was worse and we patch tested them. Typically, results showed they had contact dermatitis, so we modified their treatment and they got better.

**Dr. Siegfried:** While I agree that dupilumab does not have proven efficacy in contact dermatitis, there are a growing number of reports on the subject. Improvement has been reported more often than worsening. Although we have yet to determine which allergens may be more or less responsive to Th2 blockade, a trial of dupilumab can benefit some patients, especially adults with secondary contact dermatitis.

**Dr. Zirwas:** In the literature, the data are certainly mixed. There are some case reports showing that dupilumab is effective in patients with contact dermatitis and some showing it is ineffective.7 The problem is that in many studies showing dupilumab works in patients with contact dermatitis, the benchmark criterion defining the condition was a positive skin patch test. In these reports, if a patient had a positive patch test and was treated with dupilumab and got better, that patient was characterized by the authors as having contact dermatitis responding to dupilumab.

But it’s not that simple. I patch test dozens and dozens of bad atopics every year. The vast majority of the time, when patients have a positive patch test and I have them avoid the allergen, they don’t get better. I then treat them for AD, and they do get better. In these patients, what is really going on is that they have AD and a positive patch test that is not relevant to their dermatitis. When they get better on dupilumab, it is not because the dupilumab worked for contact dermatitis, it is because the dupilumab worked for AD.

**Dr. Siegfried:** By the same token, if they have a negative patch test, it doesn’t mean they don’t have contact dermatitis.

**Dr. Zirwas:** Exactly. A positive patch test doesn’t mean someone has contact dermatitis, and a negative patch test doesn’t mean they don’t. The only way to definitively diagnose contact dermatitis is to have someone avoid an allergen and get better, then re-expose them to the allergen and see their dermatitis return. A positive patch test is not even required in many cases.
Let’s take an example. You have a 50-year-old man who has had a rash for 3 years on his upper back, flank, and anterior thighs. He has a positive patch test to fragrance, biopsy shows spongiosis, he has no history of childhood rashes, no other allergies, no hay fever, and no asthma, but he does have a second cousin who is allergic to cats. According to the Hanifin and Rajka criteria, that person has AD, and according to the patch test, they may also have contact dermatitis. Now, which is it? Do they have one or the other, or both? They certainly don’t have classic AD. The only way to find out if it is contact dermatitis or AD is to do allergen avoidance and see if they get better. If they do, we have confirmed contact dermatitis and don’t have to do anything else. If they don’t, then we have essentially ruled out contact dermatitis and initiate a trial of dupilumab. If they get better, we still don’t know if they truly have AD that improved thanks to dupilumab or if they have dermatitis NOS that was helped by dupilumab.

What I’m getting at is because dupilumab has worked for me in essentially every case of “noncontact dermatitis” that I’ve treated—whether classic atopic dermatitis or not—I don’t know if I should be thinking, “Gee, there are a lot of people with adult-onset dermatitis that gets better with dupilumab, and as it gets better on dupilumab, it must be adult onset AD” or if I should be thinking, “Well, because it isn’t classic atopic dermatitis, it must be dermatitis NOS, and this must mean that dupilumab works for dermatitis NOS and not just for AD.” I don’t know which one of those is the right answer. I also don’t know how you would answer that question right now.

**DERMATOLOGY TIMES:** This has been a terrific discussion. We want to thank you all for your insights. I hope that our audience is able to take away some helpful information from our discussion to inform their practice’s approach to the management of moderate-to-severe AD.

### REFERENCES