SKINCARE PLAYS AN increasingly important role as an adjunct to prescription treatments for acne and rosacea, says an expert. And more than ever, consumers are demanding “clean” skin-care products and regimens, she adds.

“Clean skincare has become a very popular topic for patients. They want natural, cleaner alternatives,” says Diane S. Berson, M.D., associate professor of dermatology at Weill Medical College of Cornell University and assistant attending dermatologist at NewYork-Presbyterian Hospital.

A growing population of patients prefers products without parabens, formaldehyde, propylene glycol, sulfates, phthalates and fragrances.

“Some patients feel that these ingredients can be toxic endocrine disruptors, or that they might be carcinogenic or environmental hazards,” she says.

Researchers often sample the skin of patients with atopic dermatitis and psoriasis with biopsies. While useful for the information they provide, biopsies are invasive, cause pain and scarring. The need for multiple or sequential skin biopsies can be particularly challenging, according to Emma Guttmann-Yassky, M.D., Ph.D., the incoming chair of dermatology at the Icahn School of Medicine at Mount Sinai and the Mount Sinai Health System.

Dr. Guttmann-Yassky was happy to adapt a noninvasive way of using a type of tape strip to sample the skin. The strips not only rival biopsies for accurately detecting distinct immune and barrier signatures in lesional and nonlesional atopic dermatitis and psoriasis skin. Tape strips also revealed a single gene biomarker, nitride oxide synthase 2 (NOS2), that differentiates atopic dermatitis from psoriasis with 100% accuracy, according to the study published July 21 in the Journal of Allergy and Clinical Immunology.1

“Clean’ SKINCARE TREND GROWS

JOHN JESITUS | Staff Correspondent

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“Some patients feel that these ingredients can be toxic endocrine disruptors, or that they might be carcinogenic or environmental hazards,” she says.

Although the COVID-19 pandemic has severely tested dermatologists’ improvisational skills, many practices are steadily recovering. In this regard, successful strategies include communicating clearly, rearranging workflows quickly and embracing telemedicine wherever possible.

According to an international survey of 1,392 physicians in eight specialties, dermatologists have been among the most severely affected by the pandemic. As of mid-April, 58% of dermatologists surveyed reported a significant drop in patient volume, with an average decrease of...
Transformations in practice and care

by MIKE HENNESSY, SR

As we transition into autumn — a season that traditionally represents change and transformation — I think we can all agree, we’re still deep into navigating a significantly changed and changing landscape. Practices as well as professional and personal lives have shifted — possibly for good. However, while we navigate new practice dynamics, therapeutics continue to advance through the pipeline providing hope for improving the quality of many patients’ lives.

In this month’s issue, we’ve taken a look at the way in which you’ve experienced the impact of the pandemic on your practices. While many physicians say they’re in recovery mode, a survey suggests that patient volume has dropped to 58% (1). Some experts say that “normal” is a thing of the past. That may be, but, we still continue to report on advances and developments in dermatology. There are bright and growing areas, despite the adversities.

In atopic dermatitis and psoriasis, clinicians continue to make new discoveries about disease pathogenesis, which has led to the potential to noninvasively sample skin to determine more accurate treatment courses for patients (2). Investigators have found that intermittent biologic use may not significantly impact a patient’s overall treatment (34). In addition, experts say that stopping presurgical biologic treatment may not impact infection risk (35). Several drugs are demonstrating positive impacts on quality of life. Lebrikizumab (Eli Lilly) has achieved rapid, dose-dependent improvement across a range of atopic dermatitis metrics and has been well-tolerated by patients (31). And, lidocurizumab (Bumya, Sun Pharma) has demonstrated efficacy and safety in psoriasis treatment, lasting up to five years (36).

Research in skin cancer treatment has found that curettage and cryotherapy and electodesiccation and curettage have comparable cure rates in treating nonmelanoma skin cancers (38) and that Nano-Pulse Stimulation technology (NPS, Pulse Biosciences) is having a positive effect on the treatment of nodular basal cell carcinoma (nBCC) (39).

Over the coming months, we’ll continue to share therapeutic updates as well as the experiences and suggestions of your colleagues for how to successfully adapt to the new normal as we move toward a new year with new challenges and, hopefully, opportunities.

MIKE HENNESSY, SR., CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES’ PARENT COMPANY, ALN LIFE SCIENCES.
An IL-23 inhibitor for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy\(^1\)

**NOTHING IS EVERYTHING**

Nothing less than the opportunity for durable skin clearance.\(^1\)

For your patients, that’s everything.

**DURABLE**
Most patients achieved PASI 90 at Week 16 and maintained it at Week 52.\(^1,2\)

**RAPID**
Co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16,\(^1,2\) including response 4 weeks after first dose.\(^2,3\)

**CLEAR**
The majority of patients achieved PASI 100 at Week 52.\(^1,2\)

**4 DOSES PER YEAR**
Reliable 3-month dosing after 2 initiation doses at Weeks 0 and 4 (150 mg per dose).\(^1\)

**SAFETY CONSIDERATIONS\(^1\)**
SKYRIZI may increase the risk of infection. Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Avoid use of live vaccines in SKYRIZI patients.

Please see additional Important Safety Information on the inside spread.
Please see the Brief Summary of the full Prescribing Information on the last page of this ad.
**ACHIEVEMENTS AT WEEK 16 IN ULTIMMA-1 & ULTIMMA-2 (NRI)**

<table>
<thead>
<tr>
<th>PASI 90 at Week 16</th>
<th>sPGA 0/1 at Week 16</th>
<th>PASI 100 at Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ULTIMMA-1</strong></td>
<td><strong>ULTIMMA-2</strong></td>
<td><strong>ULTIMMA-1</strong></td>
</tr>
<tr>
<td>75% (229/304)</td>
<td>88% (267/304)</td>
<td>36% (109/304)</td>
</tr>
<tr>
<td>5% (5/102)</td>
<td>8% (8/102)</td>
<td>0% (0/102)</td>
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<tr>
<td><strong>ULTIMMA-2</strong></td>
<td><strong>ULTIMMA-2</strong></td>
<td><strong>ULTIMMA-2</strong></td>
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<tr>
<td>75% (220/294)</td>
<td>84% (246/294)</td>
<td>51% (149/294)</td>
</tr>
<tr>
<td>2% (2/98)</td>
<td>5% (5/98)</td>
<td>2% (2/98)</td>
</tr>
</tbody>
</table>

**CO-PRIMARY ENDPOINTS (P<0.0001)**

**SECONDARY ENDPOINT (P<0.001)**

**CONSISTENT PASI 90/100 RATES AT 2.5 YEARS IN OPEN-LABEL EXTENSION**

**INTEGRATED RESULTS FROM ULTIMMA-1 AND 2—ALL DATA ARE AS OBSERVED**

Participants received treatment at Week 0, Week 4, and every 12 weeks thereafter.

**STUDY DESIGN:**

The data presented here are from UltIMMa-1 (N=506) and UltIMMa-2 (N=491), which were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and every 12 weeks thereafter.

**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

**Infection**

- SKYRIZI (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

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

**Pre-Treatment Evaluation for Tuberculosis (TB)**

- Prior to initiating treatment with SKYRIZI, evaluate for infection. Do not initiate treatment with SKYRIZI in patients with active TB. Do not initiate treatment with SKYRIZI in patients with a history of TB infection and consider treatment in patients with latent or active TB for whom an adequate course of antituberculosis therapy is completed.

**EXPLORE LONG-TERM DATA AT VIEWTHEDATA.COM**
MAINTENANCE OF RESPONSE

**AT WEEK 52**
In the randomized controlled trials, among patients who achieved PASI 90 or PASI 100 at Week 16, level of response was maintained at Week 52 by 88% (n=398/450) and 80% (n=206/258), respectively.¹

**AT WEEK 136**
In an observed analysis,* among patients who achieved PASI 90 or PASI 100 at Week 52 and had available data at Week 136 in the open-label extension, level of response was maintained at Week 136 by 94% (n=375/398) and 82% (n=232/282), respectively.⁴

*Analysis conducted 8/6/2019.

KEY VARIABLES (AS MEASURED EVERY 12 WEEKS THROUGH WEEK 172) OF OLE
sPGA 0/1, sPGA 0, PASI 75, PASI 90, and PASI 100

OLE LIMITATIONS: In an open-label extension, there is potential for enrichment of the long-term data in the remaining patient populations since patients who are unable to tolerate or do not respond to the drug often drop out.

STUDY DESIGN: The data presented here are a sub-analysis of LIMMitless (OLE) and include only patients from ultIMMa-1 and 2 who were originally randomized to SKYRIZI, completed the RCT, and enrolled in the OLE. LIMMitless is an open-label extension for which patients who completed either ultIMMa trials, IMIevento have been eligible to participate.

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

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years) was similar to the rate observed during the first 16 weeks of treatment. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis and herpes zoster.

### Specific Adverse Drug Reactions

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

- **Immunizations**: Do not administer SKYRIZI to patients with active TB. Avoid use of live vaccines in patients treated with SKYRIZI.

- **Live Vaccinations**: SKYRIZI is contraindicated in patients with active TB or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and functional consequences of exposure to SKYRIZI by the nursing infant are unknown. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur in their infants.

### WARNINGS AND PRECAUTIONS

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

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ACNE
'Clean' skincare trend grows
Sustainable, plant-based skincare is a billion-dollar market

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Pandemic patient volumes
Dermatologists have seen 50% drop

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WE WILL CHALLENGE THE STATUS QUO.
WE WILL DELIVER ON OUR PROMISES.
"This court was the first to create the ‘professional standard’ of disclosure..."

I warned my patient – was it enough?

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. Lose has surgically removed an invasive squamous cell carcinoma from the face of his patient Ms. Doe. He has warned her about the risks of infection, bleeding and scarring. The surgery is performed without difficulty. Unfortunately, some five days after surgery, Ms. Doe develops cellulitis and ultimately sepsis.

After a lengthy hospitalization, loss of her job and a newly developed fear of physicians, she sues Dr. Lose for negligence. The crux of her case is based on the fact that, although she was warned about the possibility of infection, Dr. Lose should have explained to her that infection could lead to sepsis and possibly death.

Should Dr. Lose have discussed that infection can lead to sepsis? Was his warning about the risk of infection enough? What should he have disclosed during his informed consent with his patient?

There are currently two different standards as to what a physician must disclose to a patient; they are:
- a physician-centered standard, and
- a patient-centered standard.

The first court to express a physician-centered standard was Natanson v. Kline in 1960. In this case, the patient underwent cobalt radiation therapy to prevent the return of her breast cancer, after a mastectomy. The patient sued her physician, claiming that the physician was negligent in not warning her of the risks of radiation therapy, which resulted in severe injury. The court stated that the physician must “disclose and explain to the patient in language as simple as necessary the nature of the ailment, the nature of the proposed treatment, the probability of success or of alternatives, and, perhaps, the risks of unfortunate results and unforeseen conditions within the body...” This standard is the language most courts use today in defining what must be disclosed to get informed consent.

This court was the first to create the “professional standard” of disclosure when it held that the “duty of the physician to disclose...is limited to those disclosures which a reasonable medical practitioner would make under the same or similar circumstances.”

In 1972, three different courts modified the Natanson standard by holding that the disclosure standard was what a patient would reasonably need to know in order to make an informed decision rather than what a reasonable physician would disclose. This reasonable patient standard — more than the reasonable practitioner standard — would give a patient even more autonomy and right of self-determination. It should be noted that the patient-centered standard remains the minority view in this country.

In Wilkinson v. Vesey, a patient underwent radiation therapy after the physician diagnosed probable lymphoma. As a result of the radiation therapy, the patient’s skin on his chest and back necrosed and eventually required plastic surgery. The patient sued the physician, claiming the physician failed to disclose all possible risks of the radiation therapy, thus failing to get the patient’s consent.

The Wilkinson court criticized the physician-centered standard on what to disclose. The Wilkinson court noted that the requirement of expert testimony undermines the fundamental principle underlying the doctrine of informed consent, which is the patient’s right to do as she wishes with her own body. The court held, “The requirement that a patient obtain an expert to evaluate the disclosures...undermines the very basis of the informed consent theory — the patient’s right to be the final judge to do with his body as he wills.”

It would seem likely that Dr. Lose, in a “reasonable medical practitioner” jurisdiction, is not likely to lose his case. In a “reasonable patient” jurisdiction, the final conclusion is not so clear.
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INCLUDES:
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~ Dina N. Anderson, MD
Dermatologist, Clinical Instructor
Mount Sinai, New York City

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“Retinol remains the most effective antiaging ingredient in cosmeceuticals.”

The retinoid revolution

by ZOE DIANA DRAELOS, M.D.
Dr. Draelos is a consulting professor of dermatology, Duke University School of Medicine, Durham, N.C.

What are carotenoids and how are they related to Vitamin A?
Carotenoids encompass several substances including beta-carotene, zeaxanthin, lutein, and lycopene, all of which are finding their way into skin nutritional supplements. Vitamin A is only found in those carotenoids that can be converted to retinol, which is essential for vision, gene transcription, and immune function. Retinol can modulate retinoid receptors in the skin, making it the most effective of the OTC topical vitamin A derivatives. Other derivatives, such as the commonly used retinyl palmitate, are not directly capable of binding with skin retinoid receptors; however, they can function as antioxidant preservatives by preventing oxidation of lipids present in moisturizer formulations.

Zeaxanthin and lutein are isomeric with one another, but are not forms of vitamin A. Lutein is a major antioxidant in the macula lutea of the eye with decreasing levels leading to macular degeneration, a major cause of blindness. Lutein absorbs blue light and appears yellow in low concentration and orange-red in high concentration, but it is not used in skincare because it discolors formulations.

Lycopene is also not a vitamin A as it is not a source of retinol. It is a very important oral antioxidant, found in tomatoes, ketchup, and watermelon, but it is finding its way into some skincare formulations. It, too, is a pigmented molecule, which makes formulation difficult.

While zeaxanthin, lutein, and lycopene are not able to topically modulate cutaneous retinoid receptors, they are important dietary skin antioxidants. These ingredients are frequently found in skin vitamins, but it is not necessary to purchase an expensive supplement. One tablespoon of ketchup or a fresh tomato each day will provide all the zeaxanthin, lutein, and lycopene necessary for skin health!

Why is there so much interest in Vitamin A in skincare products?
There is great interest in topical vitamin A because of the appearance successes seen with prescription tretinoin. Tretinoin is the only prescription product demonstrated to reduce facial fine lines and wrinkling. Retinol, the vitamin form, is converted in minute quantities to tretinoin in the dermis; thus, an OTC ingredient might be able to mimic the effects of prescription tretinoin. This is why retinol is found in many antiaging formulations.

Retinol is a relatively inexpensive ingredient with great manufacturing challenges. It is a potent antioxidant best produced in an oxygen-free environment and packaged to minimize oxygen exposure. Other antioxidants are added to retinol formulations to assist in stabilization. Unfortunately, retinol possesses some skin irritation issues, although to a lesser degree than tretinoin. Retinol remains the most effective antiaging ingredient in cosmeceuticals.

How can retinoid irritation be minimized?
Irritation is clearly the most challenging patient issue with retinol and tretinoin. Efficacy can be had, but patients find getting there sometimes impossible. Before beginning retinoid antiaging treatment, it is important to optimize the skin barrier. Be sure all dermatologic disease, such as seborrheic dermatitis, rosacea, or acne, is treated. Switch the patient to a mild facial cleanser (CeraVe or Cetaphil Gentle Cleanser) for use morning and evening. Remove all facial exfoliants, toners, and scrubs from the patient’s cleansing routine. Use a good moisturizer as the only skincare product morning and evening (CeraVe or Cetaphil Cream). Any colored cosmetic desired can be worn, but only a gentle cleanser and cream moisturizer can be used. Continue this skincare regimen for two weeks.

After the two-week basic skincare washout period, begin with the lowest strength retinoid applied every evening to a clean washed face. Be sure the face is allowed to completely dry at least 20 minutes. Apply a pea sized amount of the retinoid with one dab to the forehead, nose, right cheek, left cheek, and chin. Spread until a thin layer is achieved avoiding the moist areas of the face, such as eyes and lips. Be careful not to apply to the corners of the mouth and nose. Immediately after the retinoid is spread, apply a generous amount of cream moisturizer in the same manner as frosting a cake. Use each strength of retinoid for four weeks prior to increasing the dose.

If too much irritation occurs, it is possible to miss a dose, but the more doses that are missed, the more challenging the retinization process will become. Not all patients will be able to use the strongest dose. When irritation arises, it may be best to leave the patient at the most tolerable dose without the risk of increase.
Study finds HS associated with acne conglobata

ILIYA PETROU, M.D. | Staff Correspondent

Historically thought to be a disorder limited to the skin, hidradenitis suppurativa (HS) is now understood to have systemic manifestations and comorbidities that can significantly impact well-being and quality of life.

A recent study found a significant association between HS and acne conglobata, highlighting the systemic nature of the disorder as well as the importance of contemplating treatment strategies that can target both disorders.

Traditionally, HS was considered to be part of the "follicular occlusion" tetrad including pilonidal sinus, folliculitis decalvans, and acne conglobata; however, continued research has led to the conventional wisdom that folliculocclusion is only one of the components that drive HS.

"We understand now that HS is much more than just a cutaneous disorder affecting the skin, as HS can also cause significant scarring and is much more HS-like in their behavior," he adds.

Dr. Smith says.

For the 1,271 references found, four case-control studies remained in the final evaluation, yielding a total of 175,792 HS patients compared with 17,146,276 control cases.

A meta-analysis of the data revealed that HS was significantly associated with acne conglobata after adjustment for potential confounders. In a pooled unadjusted meta-analysis, researchers found a significantly higher proportion of patients with acne vulgaris/conglobata in HS cases compared to controls.

There are multiple clinical features which are common to both the development of HS and acne vulgaris/conglobata references follicular obstruction, dilatation, inflammation and rupture. According to Dr. Smith, common pathological mechanisms such as excessive activation of the innate immune system and increased cytokine and IL-1 release may lead to neutrophil-rich cutaneous inflammation. Moreover, IL-17 has also been shown to be overexpressed in both HS and acne vulgaris, which is thought to promote neutrophil-driven inflammation, further lending credence to the association of the two disorders.

"I feel that acne vulgaris/conglobate is in a spectrum with HS. Some patients who look like they have acne as a separate diagnosis, in fact, have HS affecting their neck/jawline/back, while other patients will simply have bad acne with comorbid HS. It is important to recognize the different groups because they need different therapies to maximize the control of their disease," Dr. Smith says.

Severe cases of acne conglobata and HS can cause significant scarring in the neck, back, and jawline regions and it is therefore paramount for clinicians to intervene as early as possible with optimal treatment strategies to help minimize these sequelae. According to Dr. Smith, the right therapy can help address the significant active disease and scarring sequelae, both of which, if untreated/undertreated, can cause a significant detrimental impact on the quality of life of patients.

Given the underdiagnosed nature of HS as well as the gradually escalating severity of HS over time, it is important to ask our moderate-to-severe acne patients if they have any symptoms of HS.

Disclosures:
Dr. Smith has the following disclosures: AbbVie: Advisory Board, Speaker, Conference Travel sponsorship; UCB: Sub-Investigator

References:
INDICATIONS AND USAGE
AMZEEQ® (minocycline) topical foam, 4% is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION

Contraindications: Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in AMZEEQ.

Warnings and Precautions

Flammability: The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

AMZEEQ is a topical foam. While systemic absorption of AMZEEQ is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

IMPORTANT SAFETY INFORMATION (cont.)

• Teratogenic effects, inhibition of bone growth & permanent tooth discoloration: Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.

• Clostridium difficile associated diarrhea (CDAD): If CDAD occurs, discontinue AMZEEQ.

• Hepatotoxicity & metabolic effects: If renal impairment exists or if liver injury suspected, discontinue AMZEEQ.

• Central nervous system effects: Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.

• Intracranial hypertension: Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.

• Autoimmune syndromes: Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue AMZEEQ immediately if symptoms occur.
THE FIRST AND ONLY TOPICAL MINOCYCLINE FOR ACNE
FOR YOUR PATIENTS WITH INFLAMMATORY LESIONS OF MODERATE TO SEVERE ACNE VULGARIS.

The minocycline you know and trust. 1
• In large, 12-week trials, Amzeeq demonstrated an improvement vs. vehicle foam in both inflammatory lesions and IGA scores. 1,2
• The most commonly reported adverse reaction was headache (3%). 1,2

The tolerability of a gentle foam. 1
• Proprietary oil-based foam vehicle contains natural moisturizing ingredients without drying agents like ethyl alcohol. 1,3†

The innovation you've been waiting for.
• Molecule Stabilizing Technology (MST)™ enables minocycline to be placed into a lipophilic vehicle for stable topical delivery. 1,4,5

IMPORTANT SAFETY INFORMATION (cont.)
• Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using AMZEEQ. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.

• Hypersensitivity reactions: Discontinue AMZEEQ immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.

• Tissue hyperpigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.

• Superinfection: Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

Adverse Reactions: The most common adverse reaction reported during clinical trials of AMZEEQ was headache.

* Caprimary endpoints at Week 12 were: Absolute change from baseline in inflammatory lesion count and IGA endpoint success. IGA success was defined as an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade improvement (decrease). IGA = Investigator’s Global Assessment. 248 patients were included if they had 20–50 inflammatory lesions (papules, pustules, nodules) and 25–100 noninflammatory lesions (open, closed comedones) and an IGA score on a 6-point scale of moderate or severe (grade 3 or 4).
† Amzeeq 4% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).


See Brief Summary of Prescribing Information for AMZEEQ on following pages.

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AMZEQ® (minocycline) topical foam, 4% BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION. PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION
AMZEQ is indicated for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older. Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEQ should be used only as indicated.

CONTRAINDICATIONS
This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within AMZEQ.

WARNINGS AND PRECAUTIONS
- Flammability: The propellant in AMZEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- Teratogenic Effects: Minocycline, like other tetracycline-class drugs, may induce bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- Tooth Discoloration: The use of tetracycline-class drugs orally during tooth development can cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline use. Use of tetracycline drugs is not recommended during tooth development. The safety and effectiveness of AMZEQ have not been established in pediatric patients less than 9 years of age.
- Inhibition of Bone Growth: All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of AMZEQ have not been established in patients less than 9 years of age. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy.
- Clostridium difficile Associated Diarrhea: Clostridium difficile associated diarrhea (CDAD) has been reported with orally administered antibiotics, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- Hepatotoxicity: Post-marketing cases of severe liver injury, including irreversible drug-induced hepatitis and fulminant hepatitis failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.
- Metabolic Effects: The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- Central Nervous System Effects: Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- Intracranial Hypertension: Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of III are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concurrent use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt neurologic evaluation is so prudent. With acute intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- Autoimmune Syndromes: Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEQ.
- Photosensitivity: Photosensitivity manifested by an exuberant sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEQ did not induce phototoxicity or photosensitization in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV/A/B treatment) while using minocycline. If patients need to be outdoors while using AMZEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with AMZEQ at the first evidence of sunburn.
- Serious Skin/Hypersensitivity Reaction: Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythem multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEQ immediately.
- Tissue Hyperpigmentation: Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, vesicular tissue, oral cavity (teeth, mucosa, alveolar bone), sclera and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
- Development of Drug-Resistant Bacteria: AMZEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEQ, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEQ, it should be used only as indicated.
- Superinfection/Potential for Microbial Overgrowth: Use of AMZEQ may result in overgrowth of non-acceptable organisms, including fungi. If superinfection occurs, discontinue AMZEQ 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 practice. In a randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEQ or vehicle once daily for 12 weeks. A total of 1,156 subjects were treated with AMZEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (64%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.
- The most common adverse reaction reported by ≥1% of subjects treated with AMZEQ and more frequently than in subjects treated with vehicle was...
headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle. Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. The active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ were as follows (mild, moderate, severe): erythema (14.2%, 1.5%, 0%), dryness (6.8%, 0.6%, 0%), hyperpigmentation (12.4%, 2.8%, 0.1%), skin peeling (3.2%, 0.2%, 0%), and itching (3.1%, 0.8%, 0.1%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne. Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

**DRUG INTERACTIONS**
- **Anticoagulants:** Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
- **Penicillin:** Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
- **Drug/Laboratory Test Interactions:** False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**USE IN SPECIFIC POPULATIONS**
- **Pregnancy:** Risk Summary: Available data with AMZEEQ use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days. Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of the teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with AMZEEQ. In animal reproductive studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (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 birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
- **Data: Animal Data:** Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause reatralation of skeletal development of the developing fetuses. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively (750 and 500 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduct mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).
- **Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).
- **Lactation:** Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ.
- **Pediatric Use:** The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of acne vulgaris in moderate to severe acne vulgaris. Use of AMZEEQ for this indication is supported by three adequate and well controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials. Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth.
- **Geriatric Use:** Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**NONCLINICAL TOXICOLOGY**
- **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at doses up to 200 mg/kg/day, minocycline hydrochloride was associated with both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation (Ames test) or CHIGFIPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.
- **Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.
- **HANDLING:** Allow the can to warm to room temperature before first use. Shake can well before use.
- **WARNING:** Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.amzeeq.com or call 1-844-375-3673.

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QuickTAKEs

A retrospective review of patients seen in an academic dermatology clinic over a one-year period identified 20 individuals with nasal papules in association with acne.

The papules are thought to represent scarring sequelae of acne.

This condition is underrecognized and further research is needed to understand its epidemiology, pathogenesis, and management.

Case series highlights acne scarring phenotype

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Papules occurring predominantly on the nose is an underrecognized form of acne scarring that seems to disproportionately affect younger males with skin of color, reported dermatology researchers from the New York University Grossman School of Medicine, New York. In an article published first online1, researchers reported findings from a retrospective review that identified a series of 20 patients who presented with multiple papules on the nose in association with acne vulgaris.

Patients with nasal papules were identified through a review of electronic medical records between April 2018 and April 2019 by searching a photograph archive database using the terms “acne” and “nasal papules.” The patients who were included had 17 men and three females. The median age of presentation was 16 years (range 12 to 30 years) and the mean age of acne onset was 14 years (range 11 to 20 years).

Nasal papules appeared concurrently or shortly after the development of acne. The majority of patients had moderate-to-severe acne and half were noted to have concurrent acne on the nose specifically. Five patients had papules on both the nose and chin. No patients had facial or extracranial hypertrophic or keloidal scarring. Eight patients were noted to have atrophic acne scars on the cheeks.

Histopathologic examination of biopsies from five patients demonstrated dermal fibrosis and dilated thin-walled blood vessels, findings that the researchers noted were indistinguishable from those of conventional angiofibromas.

“It is not clear whether these lesions are true angiofibromas or a distinct entity with shared characteristics. Although acne has not been implicated in the development of angiofibromas, based on the data available for our patients, we do not believe that their lesions are a manifestation of any of the genetic conditions that are associated with multiple facial angiofibromas,” says Jorge Roman, M.D., lead author and dermatology resident.

Cutaneous stigmata of tuberous sclerosis were absent in all patients. None of the patients had a personal or family history of any genetic disorders.

Dr. Roman told Dermatology Times that he was motivated to undertake the review after seeing a patient with these nasal papules early during his training and finding a lack of information in the literature describing the condition. A literature search identified just two published reports in the literature describing the condition. A literature search identified just two published reports of popular acne scarring.

Dr. Roman says, “Our study reports just a small series of patients that are affected by what we believe to be a much more prevalent problem. This condition is both under-recognized and under-reported. Having been raised in a predominately Latino community in Texas, I can easily recall seeing people with these papules growing up.”

All patients in the study were Fitzpatrick skin type III, IV, or V. In this cohort almost all of the cases were seen in adolescent Hispanic males. The cohort was comprised of 17 Hispanics, two African Americans, and one Asian patient. Information on patient ethnicity was absent in the previous reports of papular acne scars; so the prevalence of this condition for this particular patient demographic was a novel finding.

Dr. Roman proposed that the paucity of reports describing the nasal papules might be related to healthcare disparities.

“Previous research has shown that racial minorities are lower utilizers of dermatologic care. It is possible that the patient demographic most afflicted by this condition face significant barriers when seeking care,” he tells Dermatology Times. “Given the dearth of information available on this condition, clinicians may not recognize it as an acne-related scarring process.”

In the published article, the authors stated that the nasal papules persisted despite conventional acne treatments such as topical antibiotics, oral antibiotics, and isotretinoin. Dr. Roman says, “Evaluation of different treatments for these papules is an area of ongoing investigation. Physical treatment modalities such as ablative laser or surgical removal seem to be the most efficacious.”

He and his coauthors hope to raise awareness of this entity in order to encourage further investigation and improve patient care.

“Early recognition and treatment can prevent the development or progression of these potentially disfiguring lesions,” Dr. Roman says.

References
These patients look for sustainable products such as plant-based essential and botanical oils, she adds. Accordingly, the market for clean skincare has grown exponentially in recent years. “It’s a billion-dollar industry that now encompasses about 25% of skincare sales,” she says. Depending on the brand, Dr. Berson says she has no problem with patients using “clean” alternatives if these products make patients feel better without making their skin worse. “But the FDA has not defined this category, and some patients can develop allergies, sensitivities and photosensitive reactions to botanical products,” she says. With that in mind, she says, effective skincare can help to mend the compromised barrier of acne and rosacea, as well as reducing inflammation, camouflaging lesions, addressing microbiome imbalances and, hopefully, minimizing the appearance of oiliness and pores.

CLEANSERS
“The purpose of cleansing is to emulsify and solubilize dirt, sebum and irritants,” she says. While surfactants can damage the stratum corneum, moisturizing synthetic detergent cleansers contain milder synthetic surfactants and impart emollient lipids. Popular acne cleansing ingredients include benzoyl peroxide, salicylic acid and hypochlorous acid. “Patients with acne and rosacea should avoid harsh scrubs and alcohol-based products,” Dr. Berson adds. “Gentle cleansing will help restore the barrier and enhance the microbiome.”

MOISTURIZERS
Moisturizers should not only help repair the epidermal barrier, but also improve tolerability of prescription topicals without compromising their efficacy. Patients with acne should use noncomedogenic moisturizers, she says. “Ingredients to look for include emollient lipids such as ceramides, humectants such as glycerin and hyaluronic acid, and anti-inflammatories such as antioxidants, niacinamide, flavooids and botanicals, which will help decrease inflammation and irritation,” she says. Additional ingredients commonly found in drugstore and private-label moisturizers include hyaluronic acid, niacinamide, thermal spring waters and botanical extracts intended to decrease inflammation.

SUNSCREENS AND MAKEUP
“All patients with acne and rosacea should be using sunscreen,” she says. Sunlight exacerbates rosacea, and oral doxycycline may increase photosensitivity. Some topical medications can cause irritation when first used, Dr. Berson says. New sunscreen ingredients include phytolases, which are liposome-encapsulated DNA repair enzymes that address thymidine dimers and affect telomere shortening. Newer sunscreen delivery systems that can help patients with acne and rosacea include sticks, sprays and gels. “These are all nongreasy,” she says. “And males, who have more sebaceous or oily skin, tend to like these because they don’t clog pores.” For women, Dr. Berson says, sunscreen powders and compacts with tinted formulas can help camouflage acne. Most mineral sunscreens consist of micronized silica, which deflects light, decreasing the appearance of pores and fine lines and camouflaging redness, she says. “As far as cosmetics, mineral makeup is the way to go if you want to reduce the appearance of oil and pores and camouflage acne.” The inorganic compounds titanium dioxide and zinc oxide can provide both camouflage and sun protection. Dimethicone cross-polymers not only hydrate and lubricate skin, she says, but also provide mattifying effects. Talc microspheres absorb oil. “Green tint underneath makeup is helpful to camouflage redness,” Dr. Berson adds.

Disclosures:
Dr. Berson has been an investigator, advisor or consultant for Aclaris, Allergan, Allmirall, Cassiopea, CLN, Crown, Evolus, Ferndale, L’Oréal, Ortho Dermatologics, Procter & Gamble, Revance, RegimenPro and Sonoma.

Reference:
Rosacea occurs across the entire spectrum of skin of color patients. Knowledge about its epidemiology is the foundation for early recognition and safe, effective treatment, says Theodore Rosen, M.D., who spoke during the Skin of Color Update virtual meeting September 12-13.

“According to some older publications, rosacea is not even seen among individuals with skin of color. Such misinformation can lead to a delay in diagnosis,” says Dr. Rosen, professor of dermatology, Baylor College of Medicine, Houston.

“Maintaining an index of suspicion for rosacea and including it in the differential diagnosis is the first step to timely identification.”

**PREVALENCE DATA**

According to a 2018 meta-analysis, rosacea had an estimated global prevalence of 5.5% among adults. Information on prevalence among U.S. patients with skin of color is available from a study examining data from the U.S. National Ambulatory Medical Care Survey for the years 1993 to 2010. Of the approximately 31.5 million rosacea visits included, approximately 2% were for black patients, approximately 2% were for Asians, and Hispanic or Latino patients accounted for approximately 4% of the visits.

“Added together, those rates suggest a prevalence of about 8% among skin of color patients, indicating that rosacea is certainly not unheard of in this group. In addition, keep in mind that the skin of color population also includes people of Mediterranean and Middle Eastern descent and representing multiple Asian countries. Individual studies report rosacea among skin of color patients residing in a range of global regions,” Dr. Rosen says.

**CLINICAL FINDINGS**

Difficulty recognizing some of the manifestations of rosacea in darker skinned patients may contribute to its underdiagnosis. However, all of rosacea’s features (ie, fixed central facial erythema, phymatous changes, flushing, papules and pustules, telangiectasia, and ocular manifestations) have been described in patients with skin of color. Rosacea in black patients may also be associated with granulomatous lesions. Dr. Rosen notes that, in particular, erythema and telangiectasias may be more difficult to detect in people with darker skin.

Because rosacea might be considered rare or non-existent in skin of color, the diagnosis may be overlooked for other diseases that are more prevalent. For example, African Americans may be misdiagnosed with systemic lupus erythematosus, dermatomyositis, or sarcoidosis, and acne vulgaris may be misdiagnosed across the spectrum of skin of color patients who present with papules and pustules.

“Careful examination and thorough history will help lead to the correct diagnosis,” Dr. Rosen says. “In most cases of rosacea, there is an initial history of excessive flushing whereas the other diseases are unlikely to be associated with flushing.”

Patient age may provide another clue for differentiating acne vulgaris and rosacea because rosacea tends to occur in older individuals, although there is overlap in the age range of patients affected by the two diseases. Additional signs for establishing a diagnosis of rosacea include a history of flushing and absence of comedonal lesions.

Dr. Rosen says that the granulomatous form of rosacea in black patients may be difficult to distinguish from sarcoidosis based on clinical appearance alone. With rosacea, however, patients tend to present with nodules located primarily around the eyes and nose, and notably patients with the granulomatous variant of rosacea are not affected by flushing and persistent erythema.

“Biopsy for histopathological examination should be considered for an accurate diagnosis,” Dr. Rosen says.

**TREATMENT APPROACH**

Medical approaches used to treat rosacea are the same for fair-skinned patients and those within the skin of color population. Laser and light therapy are also part of the armamentarium for treating rosacea-associated telangiectasias, erythema, and phyma in skin of color patients, but with the caveat that care must be taken to use the proper setting that will minimize the risk of post-treatment pigmentary changes and scarring, Dr. Rosen says.

“Laser and light interventions need to be used very judiciously and perhaps are best done in the hands of dermatologists who have experience with these modalities in the skin of color population,” he states.

Awareness and control of trigger factors also are a component of rosacea management for skin of color patients.

“It is interesting that on a global basis, many skin of color populations live in hot, humid regions, so that rosacea in these individuals may be aggravated by the environmental conditions,” Dr. Rosen says.

He adds that there is no evidence of any ethnic/racial differences in therapeutic response to the various agents used for rosacea management, but more research may be needed.

“This topic remains an open question because rigorous head-to-head trials comparing different demographic groups have not been done,” he says. “Similarly, the prognosis of rosacea also seems to be the same in fair-skinned individuals and various skin of color subgroups, although there is also a lack of long-term study data for the skin of color population.”
Phenotype-based approach advances management

CHERYL GUTTMAN KRADER, B.S. PHARM  |  Staff Correspondent

In 2017, the global ROSacea Consensus (ROSCO) panel recommended transitioning from a subtype to a phenotype approach for rosacea diagnosis, classification and management. Updated recommendations on diagnosis, classification and management aim to promote uptake of this phenotype approach and account for advances in research. To that end, the document includes prototype clinical tools that should help practitioners use the phenotype approach.1

Richard Gallo, M.D., Ph.D., Irma Gigli Distinguished Professor and Chairman, Department of Dermatology, University of California San Diego School of Medicine, San Diego, is one of seven physicians from the United States who served on the international panel. He was also a member of the National Rosacea Society Expert Committee that recently released an updated report on management options for rosacea.2

“The two sets of guidelines closely align and show consensus among experts in the field,” Dr. Gallo tells Dermatology Times. “The revised phenotype-based system for rosacea classification is an improvement that was created to better serve the needs of the individual rosacea patient. The new management guidelines acknowledge that rosacea frequently presents with multiple phenotypes. Recognizing the coexistence of several phenotypes enables better therapy.”

The consensus recommendations were developed using a modified Delphi process. Recommendations were accepted if at least three-fourths of the ROSCO panel members agreed or strongly agreed with the statements. The recommendations are divided into five sections and cover the following topics:

- burden of disease and treatment goals;
- diagnosis, classification and assessment;
- treatment;
- monitoring; and
- ocular rosacea.

The recommendations on burden of disease and treatment goals direct clinicians to assess severity and identify its burden as part of a shared decision-making approach to treatment selection.

The Dermatology Life Quality Index (DLQI) and/or a series of alternative questions are suggested to assess psychosocial and functional impact of rosacea as well as the severity of disease signs and symptoms. The section also highlights that achieving “clear” or “almost clear” skin should be the primary treatment objective.

As an aid to diagnosis, classification and assessment, the article includes tables that provide descriptions of cutaneous rosacea features and considerations for assessing the severity of minor cutaneous rosacea features. A treatment algorithm appears in an appendix to the paper.

The recommendations on rosacea monitoring emphasize the need for ongoing follow-up because rosacea is a chronic disease. In addition, they identify tolerability, cost and primary efficacy as key factors to discuss during consultations to gain understanding of patient satisfaction with treatment.

Treatment adherence is also addressed in the section on monitoring, and the recommendations include a list of issues to discuss with patients as a means to promote adherence. The topics include expectations on treatment duration, time to onset of efficacy, nonmedical interventions, need for maintenance therapy, chances of achieving clear skin and potential side effects.

In the section on ocular rosacea, the ROSCO panel identified underdiagnosis of the condition by dermatologists as a problem, and the group also cited optimal diagnosis of the condition, a description of its features, and evidence-based guidelines for ocular rosacea as unmet needs. Nevertheless, the ROSCO panel reached a consensus on descriptions of ocular rosacea features, which are summarized in a table, as well as on indications for patient referral. The latter features include blepharokeratoconjunctivitis, spherokeratitis, anterior uveitis and blepharoconjunctivitis. Based on input from the two ophthalmologists on the ROSCO panel, another table provides considerations for assessing the severity of ocular rosacea features. Dermatologists can also refer to a set of images available in an appendix to the article to aid in the identification of features of ocular rosacea and its diagnosis.

The recommendations were developed using a modified Delphi approach and cover burden of disease and treatment goals; diagnosis, classification and assessment; treatment; monitoring; and ocular rosacea.

The recommendations continue on page 25.
GETTING OTEZLA GETS EVEN EASIER

8 out of 10 commercially insured lives in the US have preferred access with no biologic step required for Otezla1

Otezla is listed as preferred, with no biologic step requirement, on:
- Aetna Prescription Drug Benefit
- Cigna Prescription Drug List
- CVS Caremark Formularies*
- Express Scripts National Preferred Formulary†
- OptumRx
- Prime Therapeutics
- UnitedHealthcare

Indicates no DMARD or biologic step-edit required

Contact your Otezla representative or visit OtezlaPro.com for a complete list of plans

*Basic, Standard, and Advanced Control Formularies.
†SafeGuardRx® Program has 1 biologic step for patients on certain Otezla® (apremilast) indications.
DMARD, disease-modifying antirheumatic drug.

INDICATIONS
Otezla® (apremilast) is indicated for the treatment of adult 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

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.
**Adverse Reactions**

- Headache: 8 (4) patients reported headache, and 6 (4) patients were discontinued due to headache.

**Warnings and Precautions**

- **Depression**: Treatment with Otezla is associated with an increase in depression. During clinical trials, patients experienced symptoms of depression, including suicidal thoughts or behaviors. Patients with a history of depression may be more susceptible to these reactions. Monitor patients closely, and contact their healthcare provider if such changes occur.

- **Weight Decrease**: Weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla. Monitor body weight regularly, and advise patients about the potential risk.

- **Drug Interactions**: Apremilast exposure may be decreased when co-administered with rifampin, a strong CYP450 enzyme inducer. Consult with healthcare providers before initiating any co-administered medications.

**Pregnancy and Lactation**

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. 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 1-877-311-8972 or visiting planningandprevention.com. Women should be advised to use effective contraception.

- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the development of milk production. Advise women not to breastfeed.

**Lab Monitoring**

- Regular monitoring is not required. Monitor patients for signs and symptoms of exacerbation or remission of severe psoriasis of the scalp.

**Lifestyle Adjustments**

- Otezla may be used as a step to systemic therapy for patients with moderate to severe scalp psoriasis who have not responded to other treatments.

- Consider modifying lifestyle factors, such as diet and exercise, to improve scalp health.

**Additional Information**

- For more information, visit OtezlaPro.com.

**Legal Information**

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For adult patients with moderate to severe plaque psoriasis

**OTEZLA SIGNIFICANTLY IMPROVES SCALP RESPONSE²,³**

**STAGE primary endpoint: proportion of patients achieving an ScPGA response at week 16**

| Otezla patients \(3x\) as likely to achieve scalp improvement at week 16 vs placebo in the STAGE study | 43.3% with Otezla® (apremilast) 30 mg BID (n=201) | VS (P<0.0001) | 13.7% with placebo (n=102) |

*ScPGA response was defined as the proportion of patients achieving an ScPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.

Results seen in an Otezla patient (scalp response)

![Baseline](image1)  
![Week 16](image2)  

ScPGA: 0  
3-point improvement in ScPGA score

'Actual clinical trial patient from STAGE. Individual results may vary.

**Adverse reactions²,³**

- The most common adverse reactions (≥5%) from weeks 0 to 16 included diarrhea, nausea, headache, and vomiting
- The proportion of patients who discontinued treatment because of any adverse reaction was 6% for patients who received Otezla 30 mg twice daily and 3% for patients who received placebo
- Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs 0%), nausea (1.5% vs 1%), and vomiting (1.5% vs 0%) in the Otezla group, compared to placebo

**IMPORTANT SAFETY INFORMATION (cont’d)**

**Use in Specific Populations**

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. 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 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk; the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition
- 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

**References:**
1. Data on file, Amgen Inc.  

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

OTEZLA® (apremilast) tablets, for oral use

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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 rare 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 reduction or suspension if patients develop 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 for alertness for the emergence of worsening 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.

Psoriatic Arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, Treatment of Psoriatic Arthritis with OTEZLA: In placebo, 1% (3/294) of subjects experienced depressive disorder. In OTEZLA, 3% (9/276) of subjects experienced depressive disorder.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, Treatment of Psoriasis with OTEZLA: In placebo, 1% (3/387) of subjects experienced depressive disorder. In OTEZLA, 3% (12/387) of subjects experienced depressive disorder.

Vomitinga (0.4%, 0.8%), Nasopharyngitis b (0.2%, 0.2%), Abdominal pain upper b (0.0%, 0.6%).

In the clinical trials, one subject treated with OTEZLA experienced a serious adverse reaction. One patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

Pregnancy

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 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Risk Summary

Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

Lactation

Risk Summary

There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfeeding infant, or the effects on breast milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OTEZLA and any potential adverse effects on the breastfed child from OTEZLA or from the underlying maternal condition.

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 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 337 subjects were 65 years of age or older. Rate of discontinuation of treatment due to adverse events of the most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.6%), diarrhea (1.8%), and headache (1.2%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse event was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

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.

Psoriatic Arthritis Clinical Trials: OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials (Studies Psa-1, Psa-2, and Psa-3) of similar design in adult patients with active psoriatic arthritis (see Clinical Studies (4.2)). Across the 3 studies, there were 1463 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titratin was used over the first 5 days (see Dosage and Administration (2.1)). Placebo patients whose tender and swollen joint counts had not improved by at least 20% were randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or placebo twice daily at week 16 when OTEZLA patients remained on their initial treatment. Patients randomized to 16 to 83 years, with an average median age of 51 years. The majority of the most common adverse reactions presented below occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). Placebo patients with psoriasis who discontinued treatment due to an adverse event was 3.9% in placebo-treated patients compared to 0.8% (3/414) treated with placebo. During the clinical trials, 0.3% (4/1414) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared to none in placebo treated subjects (0.0%). Depression was reported as serious in 0.2% (3/1414) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0.0%). Instances of suicidal ideation and behavior have been reported at a rate of 0.3% (3/1308) of subjects while receiving OTEZLA, compared to none in placebo-treated subjects (0.0%). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0.0%). Instances of suicidal ideation and behavior have been reported at a rate of 0.3% (3/1308) of subjects while receiving OTEZLA, compared to none in placebo-treated subjects (0.0%).

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.8%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Adverse Reactions Reported in 2% of Patients on OTEZLA and With Greater Than Or Equal To 10% Incidence in Placebo and Patients Treated Without OTEZLA

Diarrhea (6.1%, 1.6%), Nausea (3.0%, 1.7%), Upper respiratory tract infection (6.3%, 2.0%), Tension headache (3.3%, 0.6%), Headache (3.3%, 1.0%), Abdominal pain (2.1%, 0.6%), Vomiting (2.1%, 0.6%), Fatigue (2.1%, 0.6%), Dyspnea (1.5%, 0.3%), Decreased appetite (1.5%, 0.3%), Insomnia (1.0%, 0.2%), Back pain (1.0%, 0.2%), Headache (1.0%, 0.3%), Insomnia (1.0%, 0.2%), Sinus headache (1.0%, 0.3%).

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.8%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Diarrhea was evaluated in a Phase 3, multicenter, randomized, placebo-controlled study (PSOR-3) in adults with moderate to severe psoriasis of the scalp (see Clinical Studies (14.2)). A total of 302 subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. The most commonly reported adverse reactions that occurred at a higher rate in the OTEZLA group than in the placebo group were: diarrhea (31% vs. 11%), nausea (22% vs. 8%), headache (12% vs. 5%), and vomiting (5% vs. 2%). The proportion of subjects who discontinued treatment because of any adverse reaction during the 16-week placebo-controlled period of the study was 6% for subjects who received OTEZLA 30 mg twice daily and 3% for subjects who received placebo. Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs 0%), nausea (1.5% vs 1%), and vomiting (1.5% vs 0%) in the OTEZLA group compared to placebo.

Drug Interactions

Strong CYP450 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 Exposure to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Conclusion

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)].

OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should be provided. The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.OTEZLA.com or contact Amgen Medical Information at 1-800-772-6436.

Manufactured for: Amgen Inc.

US-DTZ-20-0528

9/29/20  9:13 AM
PDL + toxin improves symptoms

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

A combination approach using a pulsed dye laser (PDL) and intradermal injection of botulinum toxin type A (BoNTA) is safe and effectively improves erythema and disease-related symptoms, says Firas Al-Niaimi, M.D., who, with colleagues, summarized experience using this approach in a series of 20 patients with moderate-to-severe erythema and flushing.

"As with any treatment, there was variability in the magnitude of response. Overall, however, all patients benefited, and the patient satisfaction rate was high," he tells Dermatology Times. Dr. Al-Niaimi is a senior consultant dermatologist in London, UK.

Discussing the basis for combining PDL and intradermal BoNTA, he notes the limitations of PDL, which is a standard treatment for erythema and telangiectasia, and the potential for synergism with BoNTA.

"PDL can improve erythema by addressing the vascular component of inflammation, and by reducing Demodex density, it can modulate the innate immune system to reduce burning and pruritus. However, PDL treatment has a somewhat limited effect on flushing," Dr. Al-Niaimi explains. "By targeting neurogenic inflammation, BoNTA is particularly good for relieving bothersome flushing as well as pain and burning."

The patients were treated at three different centers with the same protocol over an 18-month period and seen for follow-up after three and nine months. Other than appropriate skincare products, they did not using any topical or systemic therapies for rosacea management. Patients received a series of three treatments performed every four to six weeks. The same PDL was used at all centers (VBeam, Candela). A single pass at sub-purpuric settings was performed, but the specific laser parameters were adjusted based on each patient's skin type, amount of chromophore, skin response and anatomic area.

Spot size ranged from 7 to 10 mm, pulse duration was set at three, six, or 10 ms, and fluence ranged from 7 to 10 J/cm². The intradermal BoNTA injections were administered immediately after the PDL treatment. Ten patients were treated with abobotulinumtoxinA (Dysport, Ipsen) and the others received onabotulinumtoxinA (Botox, Allergan). AbobotulinumtoxinA was reconstituted to achieve a final concentration of 100 units/mL and onabotulinumtoxinA was reconstituted to achieve a final concentration of 40 units/mL. Injections were delivered only in the area of the cheeks affected by flushing and were performed using a 30-gauge needle with spacing at 1-cm intervals. The total dose was individualized taking into account flushing severity and area.

"The efficacy of the treatment for improving erythema was objectively quantified through analysis of spectral uptake on digital images acquired using a 3D camera system (Antera 3D camera, Miravex Limited) and graded subjectively by the treating dermatologists using the six-point Clinician's Erythema Assessment Grading Scale. Patients benefited with a discernable reduction in erythema and episodes and severity of flushing lasting several months. Improvements in burning and pruritus were maintained at the nine-month follow-up visit. The reduction in flushing was relatively durable, and although it began to wane as the effect of the BoNTA dissipated, patients maintained improvement compared with baseline. The investigators suggested the benefit may be attributed to laser-induced eradication of vessels involved in flushing.

"Although it has been suggested that abobotulinumtoxinA has a longer duration of action than onabotulinumtoxinA, we did not observe any difference between the two products with respect to peak benefit or longevity in our small series of patients," Dr. Al-Niaimi says.

Side effects were generally limited to expected sequelae of the PDL treatment. A single patient developed mild purpura that resolved after 10 days.

The article presents the outcomes achieved in a small cohort of patients who were selected because they were treated with a standardized protocol and followed prospectively. However, Dr. Al-Niaimi says they have used the combination in a much larger number of patients with equally good results, and consider it a valuable treatment option for patients with concomitant flushing and fluctuating erythema.

Disclosure: Dr. Al-Niaimi has no relevant conflicts of interest to disclose.

References:
The microbiome connection to faster skin healing, less inflammation

One need to look no further than the gut to understand how the microbiome plays a role in skin repair.

"The gut epithelium renews itself at a much higher rate than that of the cutaneous epithelium," according to Ted Lain, M.D., M.B.A., dermatologist and chief medical officer at Sanova Dermatology, with practices throughout Texas and Louisiana. "Researchers hypothesized that the much higher microbial load and diversity of the gut microbiome plays a role."

There’s a high concentration of flagellin in the gut microbiome, Dr. Lain said. This hypothesis has led to discovery of the importance of pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) in skin healing. Keratinocytes continuously sample the microbiome colonizing the skin surface through a family of PRRs, including toll-like receptor 5. PRRs recognize PAMPs, initiating an innate immune response when activated.

In essence, flagellin, a PAMP, activates toll-like receptor 5, which, in turn, activates growth factor expression. The growth factors multiply on epithelial stem cells, stimulating their regenerative capacity and starting the epithelial renewal process.

BALANCE IS KEY

The microbiome relies on the balance of many different microbes and much of the commensal bacteria covering the skin are beneficial, according to Dr. Lain. "Their health-promoting properties include inhibiting pathogenic bacteria, limiting skin inflammation, and enhancing innate immunity," he said.

Dysbiosis occurs when there’s a preponderance of pathogenic bacteria, such as S. Aureus, leading to increased inflammation, altered pH and an immune response that tilts toward Th2-related cytokines, such as IL-4 and 13.

The percent of red, irritated skin that was restored by day 12 following the application of Cicalfate+ Restorative Protective Cream. This was 190% higher than the control group.
It is imperative that dermatologists consider the dysbiotic state of many of our most common diseases that we treat... and include repairing the microbiome in the treatment plan.”

Ted Lain, M.D., M.B.A., Dermatologist and Chief Medical Officer, Sanova Dermatology

“It is imperative that dermatologists consider the dysbiotic state of many of our most common diseases that we treat, such as acne, rosacea, psoriasis and atopic dermatitis, and include repairing the microbiome in the treatment plan,” Dr. Lain said.

THE ROLE OF -BIOTICS IN MICROBIOME REPAIR

Patients can get prebiotics, compounds that nourish a healthy microbiome, from food sources containing the healthy bacteria. “Probiotics are microbes intended to replace the healthy bacteria, and post biotics are bacterial by-products and remnants,” Dr. Lain said. “While much work has been done to identify useful bacteria as probiotics, individual and anatomic location variability of the microbiome precludes widely-adopted and helpful probiotic use.”

Enter the post biotic, flagellin. It can play an integral role in skin restoration by acting as a PAMP, thereby activating PRRs, such as toll-receptor 5. The resulting activation of the innate immune response, including an increase in antimicrobial peptide production, supports a healthy skin environment amenable to keratinocyte production and migration, according to Dr. Lain.

Early in-vitro studies on toll-like receptor 5 have shown promising results, showing 2.5-times faster keratinocyte migration, according to Dr. Lain.

An over-the-counter topical cosmetic that has a high concentration of flagellin and includes the novel postbiotic called C+ Restore, has demonstrated biologic activity resulting in toll-like receptor 5 activation, Dr. Lain said. “Postbiotic ingredients such as C+ Restore are the next generation of molecules that will play a big role in skin restoration,” he said. “Eau Thermale Avène’s Cicalfate+ Restorative Protective Cream is pioneering the new approach to skin repair in various conditions including post-procedure, general dermatoses and irritated skin, with proven efficacy, tolerance and faster time to skin restoration.”

In an in vitro study on complex red, irritated skin, Cicalfate+ Cream was shown to restore damaged skin from complex wounds. By day six, red, irritated skin was 40% restored after the application of Cicalfate+ Cream, which was 4-fold faster than the control group. By day 12, the red, irritated skin was 85% healed after the application of Cicalfate+ Cream — 190% higher than the control, according to Dr. Lain.

“Not only was recovery quicker with Cicalfate+ Cream, but the percent of closure was far greater than the control,” he said.

An in vivo study of 253 subjects found Cicalfate+ Cream soothes skin after several types of skin issues and procedures commonly performed in a physician’s office, including diaper rash and dermatitis, as well as superficial peels with mandelic acid, KTP laser treatment and other indications.

In a study looking at skin restoration using Cicalfate+ Cream, physicians evaluating subjects’ skin reported restoration efficacy after two days of Cicalfate+ Cream application was effective or highly effective in 73% subjects. By day 22, it was 92%. And in a study of 20 subjects receiving Er:YAG laser treatment, Cicalfate+ Cream applied over 21 days started immediately after ablation restored skin in an average 12.65 days compared to the 16.50 days in the control group.

PUTTING KNOWLEDGE TO DERMATOLOGY PRACTICE

As knowledge about the interplay among the microbiome, keratinocytes and the innate immune system develops, it’s becoming increasingly clear that supporting a healthy microbiome should be at the forefront of patient care, according to Dr. Lain.

“By including microbiome-friendly products and practices into our patients’ skincare regimens, whether their skin is compromised by disease or otherwise healthy, physicians are incorporating the latest science to ensure and support skin health,” Dr. Lain said.

Disclosure: This article is a sponsored partnership with Dr. Ted Lain and Pierre Fabre.
Dupilumab outlasts cyclosporine, data show

JOHN JESITUS | Staff Correspondent

Adults with atopic dermatitis (AD) stay on dupilumab (Dupixent, Sanofi and Regeneron) significantly longer than on cyclosporine, according to a recent study. Key reasons for discontinuation differed sharply between the two drugs, study authors add.

The chronic, relapsing course of AD requires long-term treatment to maintain remission and prevent relapses, and 10% to 13% of patients require systemic treatment, says senior author Giampiero Girolomoni, M.D. He is professor and chairman of dermatology at the University of Verona, Italy. The study appeared online July 7 in Dermatologic Therapy.

“Cyclosporine is effective in the short term,” says Dr. Girolomoni, “but it is not suitable for long-term treatment due to the unfavorable safety profile, which includes impairment of renal function.”

Conversely, dupilumab, which inhibits type 2 inflammatory cytokines interleukin (IL)-4 and IL-13, has no known organ toxicity or drug interactions. Compared with traditional systemic drugs, study authors add, dupilumab is not overly immunosuppressive and does not increase risk of viral infections.

To compare these drugs in clinical practice, investigators reviewed charts of 251 consecutive patients with AD treated with either dupilumab (149) or cyclosporine (102) at the University Hospital of Verona between January 1 and April 30, 2020. Patient visits occurred at baseline, after one month of treatment, and every four months thereafter for up to 16 months.

The overall probability of dupilumab and cyclosporine survival at 16 months was 82% and 11%, respectively (P<0.001). Mean treatment duration was 8.5 months and 5.3 months, respectively.

The most common reasons for dupilumab discontinuation were persistent clinical remission (11 patients/7.4%), lack of efficacy (seven patients/4.7%) and cutaneous side effects (four patients/2.6%). Predictors of reduced dupilumab survival included older age at diagnosis (45.5 years versus 19.3 years for those who continued therapy) and shorter AD duration (14 years versus 22.3 years, respectively).

Investigators used a Cox multiple regression model to confirm the associations between dupilumab discontinuation and both age at diagnosis and disease duration.

“These findings may be partially explained by the pivotal role of Th2 inflammation in younger patients, in contrast to mixed Th2/Th17/Th22 skewing in the elderly group,” the authors write. Late-onset AD and short disease duration could be considered predictive factors of dupilumab discontinuation, they add, although these findings could be skewed by the study’s small sample size. Adult-onset AD may be different from early-onset AD, says Dr. Girolomoni.

“Apart from possible differences in pathogenic pathways and immunologic factors,” he explains, “AD arising in adults or aged people is more frequently transient, with a duration of months. Patients at later age at AD onset and shorter disease duration are more likely to discontinue dupilumab because, paradoxically, of the good efficacy of dupilumab. They stop treatment because they are disease-free for long periods.”

Among patients who discontinued cyclosporine, the most frequent reasons were extracutaneous side effects (23.5% total) including poor tolerability, elevated blood pressure, renal dysfunction and alterations in laboratory tests. Conversely, 15.6% of patients discontinued cyclosporine after persistent remission, and 11.7% discontinued due to inefficacy.

Cyclosporine showed faster efficacy than dupilumab. Most patients on the former achieved significantly greater improvement in Eczema Area and Severity Index and other scores than did those on dupilumab in the first month of treatment. After four months, however, cyclosporine and dupilumab showed similar efficacy, consistent with other studies.

Aside from its small sample size, additional study shortcomings include its retrospective nature.

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Aside from its small sample size, additional study shortcomings include its retrospective nature.
For clinicians who treat patients with atopic dermatitis

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Drug vehicles deliver added benefits

JOHN JESITUS | Staff Correspondent

A recent review concludes that rather than being inert drug carriers, vehicles for topical atopic dermatitis (AD) treatments deliver benefits that promote barrier restoration and enhance innate immune defenses. As such, authors say, dermatologists and drug developers should consider drug-vehicle interaction in therapeutic choices, drug design and clinical trials.

“Vehicles in topical formulations play several important roles that are unique to dermatology,” says Zoe Diana Draelos, M.D., president of Dermatology Consulting Services, PLLC. Vehicles must maintain drug stability, release drugs into the skin and allow them to penetrate in active form, without entering systemic circulation.

The paper, which appeared online July 16 in the Journal of Dermatological Treatment, will impact clinicians, says Dr. Draelos. It will remind them that the vehicle is an active contributor to drug efficacy, and that the formulation should be considered as a whole when selecting the appropriate medication for a patient.1

In the past, she says, developers looked for the cheapest, simplest vehicle they could get approved by the FDA.

“So, the vehicle became a nonparticipant in therapeutic treatment,” she explains. However, for example, propylene glycol can cause stinging, burning and itching, and it damages the skin barrier.”

“A more modern approach might instead use occlusive agents, such as petrolatum, which boosts penetration by hydrating the skin. Alternatively, various carbomers set on the skin’s surface create a film that encourages drug penetration, prevents transdermal water loss and will not stick to or rub off on clothing.”

“When you decrease transdermal water loss,” she says, “you improve the environment for healing.”

AD is characterized by a broken skin barrier that confers heightened sensitivity which manifests as itching, stinging and burning. Accordingly, says Dr. Draelos, vehicles should be designed to minimize barrier damage and noxious stimuli while effectively delivering the drug.

In topical trials for AD, the vehicle effect can be particularly problematic.

“Often the term placebo is used,” authors write. “However, this is incorrect and misleading given that vehicles/topical controls are often essentially emollients with inherent therapeutic effects.”

These effects include provoking molecular-level changes that boost the skin barrier and innate responses.

Clinical-trial designs often allow concurrent use of emollients with topical medications without considering the emollients’ clinical effects.

“That increases penetration of the drug, but propylene glycol can cause stinging, burning and itching, and it damages the skin barrier.”

Dr. Draelos says that this situation makes it impossible to determine whether concomitant use of emollients improves the overall therapeutic effect or masks the effects of drugs delivered in a vehicle.

“One reason why many companies don’t want to make really nice therapeutic vehicles is because it decreases the chances of statistically separating the vehicle from the vehicle plus the active drug,” she says.

This issue is particularly pertinent, she adds, in light of recent phase 3 failures in acne where study drugs failed to separate from vehicle effects.

Different vehicle types can further obscure perceived efficacy. For example, trials of tacrolimus and pimecrolimus appear to show a stronger vehicle effect for the former’s ointment base versus the cream base of the latter. The strength of this response appears to reduce the perceived efficacy of the more potent tacrolimus.

“Given the complexities of the interaction involved,” authors conclude, “perhaps the best solution is to take a holistic approach to topical treatment, where emollient and anti-inflammatory drug combinations are codeveloped and tested together against the current standard of topical therapy in clinical practice.”

As Dr. Draelos says, “With the holistic approach, you design the vehicle to optimize the drug. So the vehicle becomes an important part of the formulation and how it performs.”

Reference:

Disclosure:
Dr. Draelos has received personal fees from various drug companies including Sanofi and Regeneron Pharmaceuticals, the makers of dupilumab.
Lebrikizumab rapidly improves quality of life

JOHN JESITUS | Staff Correspondent

In phase 2b, lebrikizumab (Eli Lilly and Company) achieved rapid, dose-dependent improvement across a range of atopic dermatitis (AD) metrics. These findings suggest a central role for interleukin (IL)-13 in the pathophysiology of AD, investigators add.

Lebrikizumab is a novel high-affinity monoclonal antibody targeting IL-13 that selectively blocks the IL-13 receptor α1 (IL-13Rα1) and IL-4Rα heterodimer signaling complex.

"Importantly," says Emma Guttman-Yassky, M.D., Ph.D., "it leaves intact the endogenous IL-13 regulation through the IL-13 receptor α2." She is the Clara Kest Professor and vice chair of dermatology at the Icahn School of Medicine at Mount Sinai in New York. She co-authored a February 26 JAMA Dermatology publication of phase 2b results and presented these data during the AAD VMX Virtual Meeting Experience October 2020, June 12-14.1,2

The clinical success of dupilumab (Dupxent, Sanofi and Regeneron), an FDA-approved anti-IL-4Rα monoclonal antibody for moderate-to-severe AD, underscores the importance of type 2 immune cytokine activation in AD pathophysiology. However, dupilumab’s inhibition of downstream signaling of both IL-4 and IL-13 make it impossible to discern which cytokine plays a more central role. Based on lebrikizumab phase 2b and other data, Dr. Guttman-Yassky and colleagues suggest that IL-13 may be the essential pathogenic mediator in AD, and that targeting it alone may achieve therapeutic responses.

Investigators randomized a total of 280 patients with moderate-to-severe AD to placebo or one of three lebrikizumab regimens:
- 125 mg every four weeks (after a 250 mg loading dose/LD);
- 250 mg every four weeks (500 mg LD); or
- 250 mg every two weeks (500 mg LD at baseline and week two)

Across all doses, lebrikizumab showed significant dose-dependent improvement in the primary endpoint, with mean week 16 reductions in Eczema Area and Severity Index (EASI) scores of 72.1% for the highest dose, 69.2% for the 250 mg every four week dose, 62.9% for lebrikizumab 125 mg every four weeks and 41.1% for placebo.

"ImportantWy, [lebrikizumab] leaves intact the endogenous IL-13 regulation through the IL-13 receptor α2." Emma Guttman-Yassky, M.D., Ph.D. Icahn School of Medicine at Mount Sinai, New York

Similar to the EASI numbers, 70% of patients at the highest dose experienced pruritus numeric rating scale (NRS) score reductions of at least four points, versus 27.3% on placebo (P<0.001). For all three doses, least-squares mean pruritus NRS reductions from baseline ranged from 35.9% to 60.6%. Conversely, pruritus scores in the placebo arm improved until week six, than gradually worsened until week 16 (mean increase 4.3%).

For patients on lebrikizumab, improvement in pruritus started early. By day two, a combined 10.5% of patients on both 250 mg doses achieved at least four-point NRS reductions. “And this continues until day seven, where already 30% of patients at the highest dose have at least four-point improvement in pruritus NRS.”

Similarly, week 16 sleep NRS scores at the highest dose fell more than 60%, versus 20.2% for placebo. “And all the drug arms show major, statistically significant changes, whereas the change in the placebo arm is not significant at week 16.”

Mean Patient-Oriented Eczeoma Measure (POEM) scores ranged from a 12.4-point reduction from baseline in patients treated with the highest drug dose versus a 5.8-point reduction for patients treated with placebo.

“Even the lowest dose shows a major improvement (−8.9 patients) compared to placebo,” Dr. Guttman-Yassky says.

Mean Dermatology Life Quality Index (DLQI) scores declined by approximately 8 to 10 points among actively treated patients, versus 5.9 points for placebo. Additionally, 39% of patients at the highest dose reported a “0” or “1” at week 16, versus 16.7% of patients treated with placebo. Patient global assessment scores followed a similar pattern.

Consistent with previous studies, lebrikizumab was well-tolerated — 2.7% of patients at the highest dose experienced moderate conjunctivitis. Ongoing phase 3 studies will further examine this adverse effect.

“But so far,” says Dr. Guttman-Yassky, “lebrikizumab has achieved a very good safety profile.” Dermira expects topline phase 3 findings in the first half of 2021.1,2

Disclosures:
Dr. Guttman-Yassky has received research funds (grants paid to Mount Sinai) from Abb-Vie, Ahmed, Asana Biosciences, Astellas, Boehringer Ingelheim, Celgene, Dermira, Desitin, EMD Serono, Escalier Biosciences, Galderma, Genentech, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Pfizer, Raptorbie, Regeneron, Sanoﬁ, Sanofi-Genzyme, SD Biopharma, and Webber Pharmaceuticals. She also serves as a consultant to Abb-Vie, Ahmed, Asana Biosciences, Astellas, Boehringer Ingelheim, Celgene, Concert DB Technologies, Dermira, DES Biopharma, EIL USA, ESL, Escalier Biosciences, Galderma, Genentech, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Pfizer, Raptorbie, Regeneron, Sanoﬁ, Sanofi-Genzyme, and Webber Pharmaceuticals.

Reference:
Tape strips outperformed skin biopsies by differentiating eczema from psoriasis with high accuracy. Like in biopsies, the tape strips for atopic dermatitis and psoriasis showed increased levels of dendritic cell and T-cell markers. Also confirmed characteristically strong Th2 expression in atopic dermatitis skin, including interleukin (IL)-13, CCL17/TARC and CCL18. Psoriasis featured higher levels of Th17-related (IL-17A/F and IL-36A/IL-36G), Th1-related (IFN-gamma and CXCL9/CXCL10), and innate immunity–related (nitric oxide synthase 2/inducible nitric oxide synthase and IL-17C) expression, according to the study.

“Many people have tried to do noninvasive techniques to sample the skin. But in many of these studies, the recovery of material from samples was small,” she says. “We have close to 100% sample recovery both for eczema and psoriasis.”

Tape stripping the skin involves applying the tape multiple times to the same area, which allows for the extraction of protein or RNA for biomarkers.

While psoriasis subjects’ skin showed marked differentiation between lesional and nonlesional tape strip samples, nonlesional atopic dermatitis skin was similar to samples in lesional areas. Like in biopsies, the tape strips for atopic dermatitis and psoriasis skin showed increased levels of dendritic cell and T-cell markers, including CD3, ITGAX/CD11c, and CD83. Tape strips also confirmed characteristically strong Th2 expression in atopic dermatitis skin, including interleukin (IL)-13, CCL17/TARC and CCL18. Psoriasis featured higher levels of Th17-related (IL-17A/F and IL-36A/IL-36G), Th1-related (IFN-gamma and CXCL9/CXCL10), and innate immunity–related (nitric oxide synthase 2/inducible nitric oxide synthase and IL-17C) expression, according to the study.

“We as dermatologists see patients in the clinic that we often debate between psoriasis and atopic dermatitis. … Having a biomarker like this, you can identify the disease easily with a single tape strip.”

Emma Guttman-Yassky, M.D., Ph.D., Icahn School of Medicine, Mount Sinai, New York

Biomarker differentiates AD from PsO FROM PAGE 1

Quick TAKES

Tape strips outperformed skin biopsies by differentiating eczema from psoriasis with high accuracy. Tape stripping the skin involves applying the tape multiple times to the same area, which allows for the extraction of protein or RNA for biomarkers. Like in biopsies, the tape strips for atopic dermatitis and psoriasis showed increased levels of dendritic cell and T-cell markers.

get the biopsies then ask ourselves, should we put them on psoriasis medication? Should we put them on an eczema medication?“ Dr. Guttman-Yassky says. “Having a biomarker like this, you can identify the disease easily with a single tape strip.”

While the most immediate use of the tape strips will be for research purposes, Dr. Guttman-Yassky says she sees the tape strips making it into the clinic. “I foresee that this will also help in diagnostics and in appropriate treatment for either psoriasis or eczema, because the treatments are so different,” she says.

Researchers obtained 20 tape strips (D-Squame, CuDerm) from each subject. The samples included lesional and nonlesional skin from 20 adults with moderate-to-severe atopic dermatitis, 20 adults with moderate-to-severe psoriasis, as well as skin from 20 healthy controls.

RNA sequencing of the strips showed the noninvasive technology detected RNA-sequence profiles in 96 of 100 samples. The tape strips of atopic dermatitis skin revealed 4,123 genes expressed that were not in normal skin. In psoriatic skin, 5,390 genes were expressed that weren’t in the controls’ skin.

While psoriasis subjects’ skin showed marked differentiation between lesional and nonlesional tape strip samples, nonlesional atopic dermatitis skin was similar to samples in lesional areas. Like in biopsies, the tape strips for atopic dermatitis and psoriasis skin showed increased levels of dendritic cell and T-cell markers, including CD3, ITGAX/CD11c, and CD83. Tape strips also confirmed characteristically strong Th2 expression in atopic dermatitis skin, including interleukin (IL)-13, CCL17/TARC and CCL18. Psoriasis featured higher levels of Th17-related (IL-17A/F and IL-36A/IL-36G), Th1-related (IFN-gamma and CXCL9/CXCL10), and innate immunity–related (nitric oxide synthase 2/inducible nitric oxide synthase and IL-17C) expression, according to the study.

“My group has been involved in a lot of biomarker studies in both eczema and psoriasis. We really replicated what we found with biopsies using tape strips,” she says. “Eczema is a Th2 (T-helper 2) driven disease and psoriasis, we know, is a Th17-driven disease.”

As for the finding that nitric oxide synthase 2 differentiates atopic dermatitis from psoriasis with 100% accuracy, Dr. Guttman-Yassky says atopic dermatitis patients have zero nitride oxide synthase 2, while the biomarker is very elevated in psoriasis.

Mount Sinai researchers will continue to investigate use of the tape strips for dermatological disease sampling. Dermatologists’ clinical use of the strips might be in a year or longer. And chances are that dermatologists would have to send the samples to a lab for analyzing, at least at first, she says.

Disclosures:

Dr. Guttman-Yassky is an employee of Mount Sinai and has received research funds from AbbVie, Celgene, Eli Lilly, Janssen, Medimmune/AstraZeneca, Novartis, Pfizer, Regeneron, Vaxx, Genentech, Galderma, Asana Biosciences, and Promius.

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Patients can regain control

Study reaffirms intermittent biologic use

JOHN JESITUS | Staff Correspondent

Stopping and restarting biologic treatment allows most patients to regain psoriasis control without experiencing unexpected safety issues, according to a recent meta-analysis. Although continuous biologic therapy provides optimal results, authors add, the study provides reassurance for patients who reject or cannot obtain continuous treatment.

“This article is a compilation and reminder of something companies have already shown us with their biologic drugs — that when you stop the drug and then restart it, you can expect most of the drugs to work pretty well again,” says Steven R. Feldman, M.D., Ph.D., professor of dermatology, pathology and public health sciences at Wake Forest University School of Medicine. He was not involved with the study, which appeared online July 8 in the *Journal of the European Academy of Dermatology & Venereology*.

Authors led by Anwar Al-Hammadi, M.D., of Rashid Hospital in Umn Hurein, Duhai, identified 18 studies that reported efficacy and safety data for intermittent use of TNF inhibitors (adalimumab [Humira, AbbVie], certolizumab pegol [Cimzia, UCB]), etanercept [Enbrel, Amgen] and infliximab [Remicade, Janssen CarePath]), interleukin (IL)-12/23 inhibitors (ustekinumab [Stelara, Janssen CarePath]), IL-23 inhibitors (guselkumab [Tremfya, Janssen CarePath]) and IL-17 inhibitors (brodalumab [Siliq, Valeant Pharmaceuticals], ixekizumab [Taltz, Eli Lilly] and secukinumab [Cosentyx, Novartis]). Following retreatment, between 60% and 95% of patients reestablished disease control as defined by each study.

“With the potential exception of infliximab,” write Al-Hammadi et al., “the efficacy and safety data published to date demonstrate that intermittent treatment, or the withdrawal and re-initiation of treatment with biologic agents, is able to reestablish disease control in a large proportion of patients, without novel safety concerns.”

Among TNF inhibitors, the proportions of patients who regained treatment response ranged from 25% who reached Psoriasis Area and Severity Index (PASI) 75 with 3 mg/kg of infliximab to 87% who achieved PASI 75 with a 400-mg maintenance dose of certolizumab pegol. Infliximab produced more infusion reactions with treatment-as-needed (11% and 9% of patients at 3 mg/kg and 5 mg/kg, respectively) than with continuous treatment (7% and 6%, respectively).

The highest response levels occurred with IL-17 inhibitors. In phase 3 secukinumab trials, 94% of patients reached PASI 75 after 16 weeks of retreatment. Additionally, 82% of patients randomized to monthly ixekizumab then re-randomization to placebo regained Physician Global Assessment (PGA) ≤1 after six ixekizumab doses. Among patients retreated with brodalumab 210 mg, 97% achieved PGA ≤1 after 12 weeks. However, the FDA-approved label for brodalumab includes a black-box warning regarding a potential link between the drug and suicide.

In real-world practice, write Al-Hammadi et al., intermittent treatment might be more feasible than continuous treatment due to lower healthcare costs, better treatment adherence and time savings for patients. However, Dr. Feldman says that based on his experience, intermittent treatment rarely occurs. When patients are prescribed treatment for severe psoriasis, the majority have such severe disease that they need continuous therapy, he says. Where the meta-analysis is useful is in situations where patients fail to heed doctors’ orders.

Some patients stopped treatment when COVID-19 first appeared because they were worried that biologic treatments might put them at increased risk. Similarly, Dr. Feldman says, when biologics were new, patients commonly stopped therapy for fear of potentially increased risks of infection and cancers — risks that subsequent research dispelled. Back when there were only two or three FDA-approved biologics available, he adds, adherence was much more crucial.

“You really didn't want the drug to fail,” he says. “Now, we have a dozen biologics.”

It is unlikely, adds Dr. Feldman, that insurers would seek cost savings by requiring intermittent biologic dosing for some patients. Instead, he says, biologic access barriers are falling.

“Eli Lilly and Company created a system that other companies were forced to follow,” he says. If a dermatologist prescribes a biologic to a commercially insured patient whose insurance covers the drug but requires a high co-pay, he explains, the drug company covers the co-pay.

“Technically, if the insurer doesn’t cover the drug, the pharmaceutical company basically guarantees that patients will get the drug at low cost,” he adds. Outside of government insurance such as Medicare, which might make it difficult to get some patients a biologic treatment, he says that for most patients, biologic access has never been better.

Reference:

Disclosures:
Dr. Feldman has received research, speaking and consulting support from a variety of companies including Gilead, Sanofi, AbbVie, Amgen, Almirall, MSD Pharma, BMS, Boehringer Ingelheim, Mylan, Celgene, Pizer, Ortho Dermatologics, Abbot, Samsung, Janssen, Eli Lilly, Merck, Novartis, Regeneron, Sanofi, Novartis, Quest, National Biological Corp., SunePhar, and SunCare Research. He also consults for other companies through OutsidePoint Global. Dr. Feldman is a consultant for various organizations. He is founder and majority owner of www.DrScore.com andstandsad part owner of Causa Research.
Quick TAKES

One study suggests it’s not necessary to stop biologic therapy preoperatively to limit postoperative infections. Another systematic review does not rule out melanoma risk associated with biologic use.

Biologic management considerations

JOHN JESITUS | Staff Correspondent

A recent study suggests that stopping biologic therapy preoperatively to limit postoperative infections may be unnecessary, while a systematic review does not rule out the possibility that biologic therapies may increase melanoma risk. Both studies, however, are hampered by a lack of quality data.

INFECTION RISK
In the first study, investigators led by Daniela Kroshinsky, M.D., MPH, of Massachusetts General Hospital and MassGeneral Hospital for Children, analyzed records of 827 patients who were given adalimumab (Humira, Abbvie), infliximab (Remicade, Janssen CarePath), etanercept (Enbrel, Amgen) or ustekinumab (Stelara, Janssen CarePath) for any inflammatory indication.

Investigators found no changes in risk of skin and soft tissue infections (SSTIs) with biologic therapy non-perioperatively (P=0.49) or in those who stopped biologic therapy preoperatively versus those who did not. Among 180 patients who underwent 218 surgical procedures, 14.5% of patients who did not stop biologic therapy preoperatively versus 6.3% of patients who stopped biologic therapy perioperatively developed SSTI risk (P=0.0049).

“Treatment with systemic corticosteroids led to an increased postoperative SSTI (rate) in this study, investigators write. “Not all biologics are governed by the same pharmacodynamic principles, so half-lives might not be the most relevant indicator of the functional level of the drug,” he says.

Interleukin (IL)-23 inhibitors’ half-lives are in <3 half-lives, 6.7%; 3 to 5 half-lives, 14.9%; or >5 half-lives, 21.4%; P= 0.52). However, disease flares occurred in one patient, three patients and one patient, respectively, in the foregoing groups. As disease severity has been shown to be associated with increased infection risk in patients with rheumatoid arthritis (RA), investigators say, stopping a biologic and developing a subsequent flare may actually increase SSTI risk more than continuing.

Accordingly, study authors suggest reevaluating current guidelines recommending that biologic agents be stopped preoperatively. It may be more efficacious, they say, to focus on minimizing corticosteroid use and other concomitant risk factors.

George Han, M.D., Ph.D., who was not involved with the study, says that due to a dearth of quality data, there currently are no clear guidelines for using biologics in the context of surgeries. He is system medical director and chief of teledermatology for Mount Sinai Health System and assistant professor of dermatology at the Icahn School of Medicine at Mount Sinai. Current guidelines guesstimate to the best of experts’ abilities, Dr. Han says.

“But the other medicines we have in the market are more targeted and persist longer,” he says. “I don’t believe it’s that reasonable to tell people to wait a whole dose or skip many months of treatment before doing elective procedures.”

MELANOMA DATA
In a separate study, Esse et al. found that compared to conventional systemic treatments, biologic use was positively associated with melanoma in patients with psoriasis (hazard ratio 1.57; 95% confidence interval 0.61-4.09), inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). Pooled relative risk (pRR) for both IBD and RA was 1.20. However, none of these differences were statistically significant. The study appeared online May 20 in JAMA Dermatology.

“There are concerns that long-term treatment with biologic therapies, such as those targeting tumor necrosis factor, could increase the long-term risk of cancer relative to people treated with conventional systemic therapy due to biologics’ impact on the immune system,” says first author Shammarke Esse, MRes, a doctoral research student in the Division of Musculoskeletal and Dermatological Sciences, University of Manchester, United Kingdom.

As melanoma is an aggressive, highly immunogenic skin cancer, he says, it should be of concern to people treated with biologics because melanoma risk increases with immunosuppression. “The evidence to date, as laid out by our study, is limited. Therefore, it is important to clarify if patients with these common inflammatory conditions who are increasingly prescribed biologic therapy are at increased risk of developing melanoma,” Mr. Esse says.


PREOPERATIVELY CONTINUES ON PAGE 36
Data support Ilumya safety

JOHN JESITUS | Staff Correspondent

Recent phase 3 data show tildrakizumab’s (Ilumya, Sun Pharma) efficacy and safety last up to five years. Together with previously released data, says a study co-author, the new data present a clear picture of what patients with psoriasis and physicians can expect from the drug.

As a group, says Alan Mendelsohn, M.D., the 13 tildrakizumab abstracts presented at the American Academy of Dermatology VMX Virtual Meeting Experience 2020 reflect the drug’s durable effects. He is associate vice president of dermatology medical affairs with Sun Pharmaceuticals.

“The large majority of patients who are getting responses within four to six months are maintaining those responses for up to four years or more. They’re also maintaining a very striking safety profile,” Dr. Mendelsohn says.

The reSURFACE 1 and 2 trials used a three-stage design with randomization for certain patient groups at weeks 12 and 28 before enrolling year-one responders into extension studies that tracked safety and efficacy through up to five years. In reSURFACE 1, the proportions of patients on tildrakizumab 100 mg who achieved Psoriasis Area and Severity Index (PASI) 75 at weeks 64 and 208 were 87% and 82%, respectively. The corresponding reSURFACE 2 figures for tildrakizumab 100 mg at weeks 52 and 196 were 92% and 85.7%.1,2

Dr. Mendelsohn says that the phase 3 data allow physicians to tell patients confidently that if they demonstrate a good response within four to six months of starting tildrakizumab, the effect likely will last four to five years for them; they need not worry about switching drugs or watching for increased risk of numerous adverse events.

The fact that the drug is physician-administered also helps providers monitor safety.

One abstract showed that when PASI 75 responders go off drug, 43% to 46% maintain their effect for an entire year.3

“Particularly in the days of a pandemic such as we’re in, that’s extraordinarily important for patients to know,” he adds.

Combined with tildrakizumab’s label, says Dr. Mendelsohn, the long-term phase 3 data provide reassurance versus labels of some other systemic psoriasis drugs. Tildrakizumab has no black-box warning or signals regarding congestive heart failure, malignancies or suicides.

The durability of tildrakizumab responses and the fact that most patients see significant improvements over placebo four weeks after a single dose also will make physicians’ and patients’ lives easier, he adds.

“Our approach has been patient- and healthcare provider-centered. We are trying to come up with the most cost-effective management with the most important mechanism of action, which is interleukin (IL)-23,” Dr. Mendelsohn says.

One abstract that traced correlations between short- and long-term responses showed that within four weeks of treatment, the average patient can expect a 42% to 45% PASI reduction.4 In phase 3, Dr. Mendelsohn says that the patients began separating into bands of improvement (50-74%, 75-89% and 90-100%) by week 12 and remained there through four years. The average patient will be approximately 41% better within a month, 70% better within eight weeks and 90% to 95% better by week 28, he says.

“The flipside is, we feel very confident in being able to say to patients and healthcare providers, we can tell within 12 to 16 weeks after you start this drug if a patient will or won’t respond. We want to be as transparent and cost-effective as possible because in the end, that’s going to benefit the patients and healthcare providers,” he says.

Disclosure:
Dr. Mendelsohn is a associate vice president of dermatology medical affairs, Sun Pharmaceuticals.

References:

Disclosures:
Dr. Mendelsohn has served as an investigator, consulted to and spoken for Abbvie, Amgen, Bausch Health, Celgene, Galderma, Regeneron, Lilly, Novartis, Janssen, LEO Pharmaceuticals, MDC2, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, SanofiAventis, SunePharma and UCSF. Dr. Mendelsohn reports nonfinancial financial interests.

References:

Preoperatively pausing biologic unnecessary for limiting post-op infections

2019. Ultimately, seven cohort studies met inclusion criteria. These studies included 34,029 biologic-treated patients and 135,370 biologic-naïve patients treated with conventional systemic agents.

Esse et al. write that to the best of their knowledge, theirs is the first systematic review and meta-analysis of melanoma risk associated with biologic-naïve patients for comparison purposes. However, investigators found only one psoriasis study (2,285 patients, versus 3,604 controls) and two IBD studies that met inclusion criteria. “The small number of studies eligible for inclusion meant that the pooled risk estimates were likely to be disproportionately affected by single studies,” write Esse et al.

“Based on the limited evidence to date,” Mr. Esse adds, “clinically meaningful increase in risk cannot be ruled out. Population-based cohort studies, adjusting for key risk factors, are urgently required to clarify this risk before any recommendations can be made.”

Disclosures:
Dr. Esse has served as a consultant, speaker, or speaker for Abbvie, Amgen, Bausch Health, Celgene, Galderma, Regeneron, Lilly, Novartis, Janssen, LEO Pharmaceuticals, MDC2, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, SanofiAventis, Sun Pharma and UCSF. Dr. Esse reports nonfinancial financial interests.

References:

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Trial compares NMSC destructive techniques

ILYA PETROU, M.D. | Staff Correspondent

There are several different treatment approaches currently being used to address low-risk nonmelanoma skin cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). A recent study found that curettage-cryosurgery and curettage (C&C) and electrodesiccation and curettage (ED&C) are two common techniques that have comparable cure rates after a one-year follow-up period, underscoring the sound therapeutic benefit of both treatment approaches.

Of all nonmelanoma skin cancers, BCC comprises approximately 75-80% of these lesions and SCC comprises approximately 20%, experts say. Both are associated with significant morbidity, aesthetic concerns and financial burden. Numerous treatment approaches including surgery, topicals, photodynamic therapy (PDT) and destruction have shown efficacy in clearing these minimally invasive tumors. ED&C is the most common procedure used for minimally invasive BCCs and is recommended as a first-line treatment for these tumors. C&C is the most commonly used technique for minimally invasive SCCs and is recommended as a first-line treatment for these lesions.

In a recent multicenter, prospective, comparative study, Suzel Fournier, M.D., from the oncology division of the CHU of Quebec, University of Laval Research Center, Quebec, Canada, and colleagues, evaluated the cure rates of minimally invasive BCC and SCC lesions when using C&C or ED&C in a cohort of 100 adult patients. Study participants were randomized 1:1 to receive either C&C and ED&C treatment, with cure rates evaluated at six, 12, 18 and 24 months, and aesthetic appearance of scars at 12 months post procedure. Evaluated on a scale from 1-10, the aesthetic appearance of the scars was assessed using the Patient and Observer Scar Assessment Scale (POSAS), which combines the assessments of both physician and patients. The average age of patients receiving C&C (n=53) and ED&C (n=47) treatment was 74 and 77 years, respectively.

Results showed that at the 12-month follow-up, only one patient had a recurrence of cutaneous carcinoma in the C&C cohort (98% cure rate), while no recurrence occurred in the patients treated with ED&C (100% cure rate), statistically demonstrating non-inferiority of the C&C technique, and achieving the primary outcome goal. The aesthetic appearance of scars also showed better results with the C&C approach at the 12-month follow-up, however this was not statistically significant. No other recurrences were recorded in either study group at the 6-, 18- and 24-month follow-up time points.

Patients’ evaluation of the aesthetic appearance of scars as reflected in the mean POSAS score was 1.39 and 1.50 in the C&C and C&E patient groups, respectively. Data also showed that a global score of 1 (best possible score) was recorded by 74% and 66% of the C&C and ED&C groups, respectively. No other recurrences were recorded in either study group at the 6-, 18- and 24-month follow-up time points.

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According to the researchers, this is the first clinical study evaluating and comparing the efficacy of C&C and ED&C with respect to cure rates and aesthetic appearance of scars for low-risk BCC and SCC tumors.

“Our study tends to demonstrate that C&C provides a high cure rate for minimally invasive basal and squamous cell carcinomas. These findings are comparable to other studies with similar protocols, but longer-follow-ups. We’ve demonstrated that the C&C technique seems noninferior to the C&E method found in main guidelines, and as such we believe that it should be investigated more thoroughly as a first-line therapy,” the study authors wrote.

Regarding aesthetic scar outcomes, the researchers said that future trials could include more objective measurements for scar assessment such as Narrow-Band Spectrophotometry, Tissue Ultrasound Palpation System, and Cutometer Skin Elasticity Meter in order to help minimize potential information bias due to the subjective assessment of scars. In addition, a larger patient study cohort could also help in evaluating the different scars based on anatomical location in future studies.

Disclosures: The authors report no relevant disclosures.

Reference:
NPS shows positive results

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Accumulating data show promise for Nano-Pulse Stimulation technology (NPS, Pulse Biosciences) in the treatment of nodular basal cell carcinoma (nBCC) and cutaneous non-genital warts. The results were presented at the 2020 virtual meeting of the American Society for Laser Medicine and Surgery, Christopher Harmon, M.D., who practices Mohs surgery and aesthetic dermatology in Birmingham, is an investigator in the nBCC study.

“Nodular BCCs are characterized by discrete large or small nests of basaloid cells in the papillary or reticular dermis,” he says. “Because of the varying degrees and unknown penetration of these deep cellular ‘nests,’ treatment typically requires surgical excision with wide margin control. NPS is exciting because early evidence indicates it can eliminate nBCCs with minimal scar- ring compared with conventional treatment.”

TARGET SPECIFICITY
NPS is performed using a treatment tip containing a microarray of needles that deliver high amplitude, ultrashort electrical bursts to target lesion cells in the epidermis to deep dermis. The energy pulses cause transient nanoporation of the outer cellular membrane, altering the function of internal cellular organelles, including mitochondrial membrane and endoplasmic reticulum.

This disruption ultimately leads to regulated cell death without any thermal effect or damage to surrounding acellular skin structures. In addition, the treatment is thought to stimulate an adaptive immune response that may contribute to clearing malignant lesions and warts.

NODULAR BCC OUTCOMES
The nBCC pilot study enrolled seven patients with a non-facial nBCC. They first underwent a pretreatment 3-mm biopsy for diagnostic confirmation and a blood draw to identify evidence of an immune response. Treating only a portion of the tumor allowed researchers to validate the effectiveness of NPS through the histopathological examination, Dr. Harmon says.

As enrollment progressed, NPS energy settings were titrated down to find the “sweet spot” providing an optimal balance of efficacy and safety. The first two patients were treated with 15.5 J of energy (310 mJ/mm²). The energy was decreased by 50% for the next three patients to 7.7 J (155 mJ/mm²), and then lowered by another 50% (3.9 J, 75 mJ/mm²) in the last two cases.

“We found that all of the energy levels were 100% effective. While tumor remained in the untreated area, the NPS-treated zones were consistently clear of nBCC. The biopsies also showed no clinical or histologic evidence of dermal scarring in the patients treated with the two lower energy settings,” Dr. Harmon says. “We were also encouraged to see infiltration of CD8+ T-cells in the untreated area in some histologic samples, which supports the idea that NPS induces a host immune response that may be part of its mechanism for tumor clearance.”

Based on positive findings of this early feasibility study, ongoing and future planned studies will further evaluate the two lower NPS energy settings of 75 or 155 mJ/mm² to determine if treating the entire visible nBCC will achieve the study endpoint of histology-confirmed BCC elimination.

Although the study is enrolling patients with nBCC, Dr. Harmon believes NPS will also be studied as a minimally invasive option for clearing any BCC classified as low risk according to NCCN guidelines.

“We chose it to study nodular lesions because superficial BCCs may be removed entirely by the pretreatment shave biopsy performed for diagnostic confirmation. Further studies might investigate its use for superficial BCCs or other low-risk BCCs on the trunk and extremities,” Dr. Harmon says.

He notes that NPS technology might also have a role for treating aggressive BCCs on the face. Because those lesions can have a very deep component, modified probes that have longer microneedles and an insulated sheath may be tested for these deeper lesions.

PROMISE FOR CHALLENGING WARTS
Interim data from an expansion of a study investigating NPS treatment for cutaneous, non-genital warts was presented by E. Victor Ross, M.D., director, Laser and Cosmetic Dermatology Center, Scripps Clinic, San Diego. According to Dr. Ross, this pivotal clinical study included additional sites, an increased number of subjects and the treatment of warts across more anatomic areas, which enabled broader use of NPS to treat this difficult group of skin lesions.

He reported preliminary findings from 27 patients who had a total of 87 warts treated. The hands (n=39), feet (n=19), legs (n=10) and knees (n = 8) were the most common sites. Efficacy was high overall, with the best clearance rates observed for warts on the knee (100%), hands (90%) and leg (80%); 10 (53%) of the 19 warts on the foot were cleared. None of the warts that were eliminated showed evidence of recurrence at follow-up 60 days post-treatment.

“Our most recent data shows a continuing trend toward elimination of the majority of warts with one or two treatments,” Dr. Ross notes. “Cells are the real target of this technology, so any parts of the skin that are more cellular in nature versus stromal in nature will be more vulnerable to NPS energy,” he adds.

The potential for viral plume generated during treatment was investigated as a safety endpoint in a sub-cohort by stationing a sensitive particulate counter near the wart as NPS energy was being delivered. The results showed no evidence that the procedure resulted in aerosol emission of particles.

“Thermal-based curative procedures may produce debris that contain dust, chemicals and infectious material. The absence of plume with NPS technology may be an important safety benefit for physicians and their patients,” Dr. Ross says.

“The next steps for the wart protocol are expected to include testing tips with longer microneedles for deeper warts and evaluating optimal follow-up treatment intervals for the subset of warts that did not clear in a single procedure session.”

Disclosures: Dr. Harmon is a consultant to and member of the scientific advisory board of Pulse Biosciences. Dr. Ross is a consultant to and received research support from Pulse Biosciences.
My experience with surface radiotherapy

by STEVEN A. DAVIS, M.D.

Steven A. Davis, M.D., is a board-certified dermatologist and Medical Director of the Dermatology & Laser Center of San Antonio. He graduated from Yale University, the University of Texas Southwestern Medical School and completed his dermatology residency at the University of California San Francisco. He is adjunct professor of Medicine/Dermatology at the UT Health San Antonio medical school.

Recent advancements have brought X-rays safely into the dermatology clinic. This past year, I have incorporated surface radiotherapy (SRT), which is approved by the U.S. Food and Drug Administration (FDA), as a treatment option for select patients with non-melanoma skin cancer (NMSC).

I have treated more than 25,000 skin cancers surgically, which is the standard of care for the vast majority of patients with NMSC. But surgery is not ideal for every patient. Patients taking prescription blood thinners or those who cannot care for surgical wounds, have a history of delayed or insufficient wound healing, an aversion to surgery, or who wish to avoid potentially deforming surgery on areas like the ears and nose may be candidates for nonsurgical options. These considerations, plus the patient’s access to care, age and family support all factor into the evaluation of surgery versus superficial radiation treatment in the dermatology clinic. It’s a classic benefit: risk analysis.

In my patient population of largely Medicare-age skin cancer patients, there is generally higher risk for stress from prolonged procedures, post-operative bleeding, delayed wound healing and inability to care fully for treatment sites. During the COVID-19 threat, the risk from prolonged face-to-face contact with the surgical team is an additional safety factor to consider.

A 0.5 cm basal cell carcinoma (BCC) on the posterior lower leg of a healthy 60-year-old patient is typically a better candidate for electrosurgery and curettage or excision than the 80-year-old patient with diabetes who has a BCC on the pre-tibial surface. A Mohs procedure closed with a flap on the nasal sidewall may be excellent for a 70-year-old patient in good health, but SRT is a good option for a patient the same age who has a cardiac condition and is on blood thinners.

In contrast to the largely unregulated office-based “X-ray” treatment machines popular up into the 1960’s, today’s SRT devices are calibrated to precisely deliver electronically generated photons directly to the skin surface, targeting the tumor area while sparing the surrounding healthy skin. Patients typically receive three treatments per week for a total of 15 to 18 treatments.

Electronic brachytherapy (eBt) offers a similar treatment option using slightly less X-ray energy and a sharper field edge that enables fewer treatments—eight to twelve—delivered twice weekly. Actual treatment time-on-tissue for both modalities averages one to two minutes per session (“fraction”), and the patient can be in and out of the office in less than 15 minutes. Both are approved by the FDA for treating NMSCs and have cure rates in the approximate range of 95%.

In my experience, many patients don’t think about radiation as a treatment for skin cancer. When we inform patients that nonsurgical SRT can be delivered in our office with far fewer treatments, they can weigh its benefits and risks against other options. In my practice, these options have included simple and advanced surgery, imiquimod and injectable 5 fluouracil. After favorable reviews of office-based SRT from some of my colleagues, I decided to add it to my practice.

I chose the RADiant system from XStrahl, an international company that makes both superfi- 
cial and orthovoltage radiation treatment devices. RADiant appealed to me because it provides both eBt and SRT modes in a single machine with a small footprint. This system does not use radioisotopes, the treatment room requires minimal shielding and the intuitive software interface holds treatment plans that are customized to each patient; thus, reducing the chance for human error.

We have now used our RADiant system for a year. There’s uniformly good patient satisfaction; treatments are brief and painless; most treatment effects, such as redness and scaling, are transient and well tolerated; and the treated sites heal with little to no scarring. While generally an attractive alternative to surgery, SRT/eBt has to be used judiciously to merit insurance coverage; while, at the same time, being cost-effective for the practitioner. Most devices on the market cost about $150K - $250K, and there are set-up fees and maintenance plans to consider.

Medicare with supplements typically covers SRT/eBt treatments. With Medicare Advantage and fully private plans, it’s wise to check with the carrier for coverage or need for pre-authorization. In terms of state regulatory requirements, SRT/eBt are well within the domain of the dermatologist, though some states place different regulatory requirements on use of eBt. If you are considering adding SRT/eBt to your practice be sure you go over your state requirements with the company from whom you are buying your device.

Given my own practice’s volume of cases and patient mix, the RADiant system’s dual mode, ease of use and reasonable start-up costs have efficiently expanded the options I can offer patients to treat their NMSCs. For patients who are apprehensive or fearful of pain or surgical complications — and otherwise meet the indications for SRT/eBt, my RADiant system has become a welcome, less stressful alternative to traditional surgery.

Disclosure:
Dr. Steven Davis purchased the RADiant System and has not been compensated for articles and presentations related to it.
This September 12,
Make it an American Dermoscopy Saturday.
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Whether or not dermatologists perform cosmetic procedures, it is important that they understand the spectrum of adverse reactions that can occur in patients with skin of color because they may see patients seeking care because of a complication, said Cheryl M. Burgess, M.D., at the Skin of Color Update virtual meeting.

With the advent of medical spas and the crossover of various specialists into cosmetic procedures, I have seen an upsurge in the number of patients with Fitzpatrick skin types IV, V, and VI who come to me because they experienced an adverse event following a treatment involving a laser or light-based device, filler or neuromodulator injection, or chemical peel,” says Dr. Burgess, founder and president, Center for Dermatology and Dermatologic Surgery, Washington, D.C.

Quick TAKES

- Proper patient selection is important for desired aesthetic outcomes.
- Patients should be counseled on appropriate cosmetic procedures for their skin type.
- Test spots may be necessary to determine potential adverse events.
- Device parameters can be adjusted for safety.

She described the types of reactions that are seen most often in skin of color and offered recommendations for minimizing risks and achieving patient satisfaction. Summarizing her top tips, Dr. Burgess says, “Careful patient selection is important for achieving the desired outcome with any cosmetic procedure, and thorough counseling should be provided at consultation on procedures that are appropriate for the individual’s skin type. Performing a test spot may be useful to determine potential adverse events with lasers and chemical peels, and laser parameters may need to be tweaked for increased safety.”

She emphasizes that it is best to start conservatively and recognize that achieving the desired outcome may require multiple sessions.

LASER AND LIGHT SYSTEMS

First and second degree burns are among the most common complications seen in skin of color patients who undergo cosmetic procedures involving a laser, and they are particularly a problem with the use of intense pulsed light devices. The burns are easily recognized by their rectangular shape, Dr. Burgess says.
The science behind skin care for sensitive skin

A bout 60% to 70% of women and 50% to 60% of men report having sensitive skin, according to research published in 2019 in Frontiers of Medicine.1 While differences in how people perceive skin sensitivity exist, most say they have sensory effects, such as itching, burning, stinging, tightness and dryness, according to the paper.

Dermatologists guide their patients on which products best address skin sensitivity symptoms, without making the problem worse or creating another problem. In some cases, the very products dermatologists recommend, like retinol for anti-aging, cause skin sensitivity issues.

“The biggest issue we have in treating patients who are sensitive is intolerance to the products themselves. The goal has been to come out with an anti-aging, skin strengthening product line that is tolerable, even to patients who can’t tolerate other products,” said Dermatologist Joshua Zeichner, M.D., director of cosmetic and clinical research in dermatology at Mount Sinai Hospital.

The problem of sensitive skin has risen dramatically in the last decade, highlighting the need for affordable, effective and scientifically-formulated and tested products designed especially for people with sensitive skin, said Hemali Gunt, Ph.D., head of clinical and scientific affairs at Burt’s Bees,2 a leader in evidence-based natural skin care. As a result of the need, Burt’s Bees developed its Sensitive Skin care line, including a daily moisturizer, facial cleanser, cleansing towelettes, night cream and eye cream.

The over-the-counter all-natural line of products earned the National Eczema Association Seal of Acceptance. Burt’s Bees’ Sensitive products have been shown clinically to improve overall skin appearance, while gently moisturizing and cleansing without causing redness or irritation.

Key ingredients that do good without harm

It’s not one ingredient, but rather a synergistic effect of several ingredients of natural origin that address skin dryness, itching and more, according to Dr. Gunt.

For example, the Burt’s Bees Sensitive Skin Care line features:

> Aloe, which has been shown in studies to help reduce visible redness and soothe skin while hydrating skin and restoring barrier function;
> Honey, a natural moisturizer with phenolic acids and flavonoid antioxidants that helps defend against free radical damage and supports healthy skin;
> Sunflower oil, which is rich in linoleic acid, an essential fatty acid in skin; and
> Rice extract, known to help reduce damage from environmental stress.

More about the science

Dermatologists want to see more than marketing claims before recommending skin care products to their patients, according to Dr. Zeichner. “As with any products, I look for companies that provide data to show that the ingredients are effective,” he said.

In research presented in 2019 at the 24th World Congress of Dermatology, Dr. Gunt and colleagues presented data showing Burt’s Bees’ Sensitive Skin Care products reinforced the skin’s epidermal barrier and improved skin hydration in Asian women with sensitive skin in a highly polluted environment.

“Our most recent work involved testing our sensitive skin care products in subjects who were exposed to high environmental pollution, which damages the skin’s moisture barrier. We enrolled subjects with heightened sensorial symptoms of stinging, burning, itching. When those subjects used our sensitive skin care products, we were able to show that response to skin sensitivity was decreased. Our products are not just occluding the skin barrier to eliminate a response to sensory stimuli, but instead using the activities of these ingredients of natural origin over a period improve skin sensitivity,” Dr. Gunt said. “We are continuing to study the products’ effects on skin sensitivity across many different populations to understand if the product line works and continues to work in a wide variety of conditions.”

The first published study on Burt’s Bees Sensitive Products showed superiority in improving overall skin appearance when compared with a dermatologist recommended synthetic regimen in subjects with eczema, rosacea and cosmetic intolerance.3

In another study published in 2019 in the Journal of Drugs in Dermatology,4 dermatologist Zoe Draelos, M.D., and colleagues performed a study evaluating the safety and tolerability of Burt’s Bees Sensitive products when used as a daily skin care routine as an adjunct in patients who were treating their rosacea with metronidazole, a prescription antibiotic. Researchers compared the Burt’s Bees’ Sensitive Skin regimen to a synthetic dermatologist-recommended regimen. They reported that subjects in the Burt’s Bees’ group experienced greater improvements in investigator global assessment of rosacea measures, including erythema, telangectasia and papules/pustules than the women using the synthetic skin care regimen.

In comparison to the synthetic brand, which is primarily composed of occlusive ingredients, Burt’s Bees Sensitive products contain natural extracts, which are known to be helpful in reducing the appearance of redness and fighting free radicals.

“The products were extremely well tolerated with no irritation. So, this is promising data and it reinforces our recommendations of these products in patients who cannot tolerate other types of anti-aging ingredients,” according to Dr. Zeichner.

REFERENCES:

Postinflammatory hypopigmentation can occur after hair removal using the short pulse 1064-nm Q-switched Nd:YAG laser whereas hyperpigmentation was more common in the past when the procedure was performed with the 532-nm systems.

“The longer 1064-nm wavelength avoids hypopigmentary changes since it bypasses the melanin in the epidermis. Its absorption deeper in the hair leads to thermal destruction of the follicle, which makes the longer wave Nd:YAG laser ideal for hair removal in skin of color,” Dr. Burgess says.

Whenever performing a laser procedure in a new patient with skin of color, however, Dr. Burgess advises performing a test spot and using a lower fluence.

“Manufacturer-recommended parameters are based on clinical trials that enrolled mostly patients with Fitzpatrick skin types I-III and some patients with skin type IV, but rarely anyone with darker skin,” she says. “When patients understand the test is being done for their safety, they are willing to accept the delay.”

**FILLER REACTIONS**

Safety data from premarketing clinical trials with various fillers did not show any increased risk of pigmentary changes or hypertrophic or keloidal scarring in patients with skin of color, although the eligibility criteria for these studies excluded patients with a history of keloids. As in patients with lighter skin types, bruising is the most common adverse event associated with filler injections in skin of color. Hyperpigmentation can also occur, particularly with the use of a serial puncture technique and faster injection times.

“Filler injections in skin of color patients are best done slowly using a linear threading technique,” Dr. Burgess says.

**NEUROMODULATOR INJECTIONS**

Dr. Burgess notes that Asian patients, particularly, request treatment for crow’s feet and glabellar frown lines. Injections into the forehead and periorcular region in these patients requires care to avoid the development of eyebrow or eyelid ptosis that will decrease the palpebral aperture.

“As people age and the laxity of the forehead and upper eyelid skin becomes more apparent, a reduced dose or avoidance of botulinumtoxinA injections is recommended to avoid eyebrow ptosis,” Dr. Burgess says.

Chemical peels Superficial chemical peels using salicylic acid, lactic acid, malic acid, or glycolic acid can be performed safely in skin of color. The use of medium and deep peeling agents, however, risks dyschromia from rapid skin exfoliation that leads to a deeper exfoliation to the lower levels of the epidermis and melanocytes with subsequent inflammation and ultimately hyperpigmentation.

Dr. Burgess says that neutralization of the acid is a technique used in medical spas to minimize risk in skin of color. However, a neutral pH is no longer an acid strength to perform chemoexfoliation.

“Chemical peels at lower pH require observation of the skin’s reaction and erythema. The end point for a peel isn’t always ‘until it frosts’ in skin of color,” Dr. Burgess says.

**Disclosure:**

Dr. Burgess receives honoraria, does clinical research for, and/or is on the advisory board of Allergan, Revance, Merz, and Prollenium.

"Manufacturer-recommended parameters are based on clinical trials that enrolled mostly patients with Fitzpatrick skin types I-III ... but rarely anyone with darker skin."

Cheryl M. Burgess, M.D., Center for Dermatology and Dermatologic Surgery, Washington, D.C.
JOIN US IN 2021

CSF Live is on hold for 2020.

2020 has certainly ushered in wholly unthinkable challenges! Like all of you, the Cosmetic Surgery Forum team has been facing them head-on and doing all we can to care for those around us and make a better community for us all.

CSF has always been committed to providing a meaningful experience for all of our participants – which includes doing our part to keep everyone safe. While we will certainly miss the camaraderie and energy of a face-to-face meeting, we truly feel this is the right decision.

In lieu of a live event in 2020, Cosmetic Surgery Forum will host sessions throughout the next 12 months offering you the same type of in-depth learning and collegial discussion you have come to expect from us. Check out our website (CosmeticSurgeryForum.com), Facebook and LinkedIn over the next few weeks for updates! We will see all of you again Wednesday, December 1 – Saturday, December 4, 2021 at the JW Marriott in Nashville, TN. Please save the date!

For more information, please contact: Natasha Mohr or Meg Housholder - info@CosmeticSurgeryForum.com - 402-697-6564
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Stem cell media boosts microneedling benefits

CHERYL GUTTMAN KRADER, B.S. PHARM | Staff Correspondent

Microneedling is an efficient method for facial skin rejuvenation, but the outcomes are augmented by using a combined approach that incorporates topical application of amniotic fluid mesenchymal stem cell derived conditioned media (AF-MSC-CM), according to a split-face comparative study.1

The study enrolled 10 patients with mild to moderate signs of photaging who underwent five treatment sessions under topical anesthesia at 2-week intervals. Microneedling with a derma-roller was performed over the entire face. Thereafter, 1 mL of AF-MSC-CM (BIO STEM CM Cell Signal Therapy Wrinkle Control kit, Bio Innovation Holdings) was applied to the right side only.

Assessments performed at 1 month after the last treatment showed significant clinical and histological improvements bilaterally. However, there was greater clinical improvement and better remodeling of dermal collagen and elastic fibers on the right side of the face.

"Although our study included just ten patients, the split-face design enabled our ability to detect a treatment benefit from adding AF-MSC-CM," says Moetaz El-Domyati, M.D., Professor of Dermatology, Minia University, Al-Minya, Egypt. "We believe that stem cell therapy represents the future for facial rejuvenation and managing aging skin."

STUDY RATIONALE
As a nonablative procedure that causes selective dermal injury, microneedling by itself is a safe and effective technique for inducing skin tightening. In addition, it is relatively inexpensive and does not involve significant downtime.

"The AF-MSC-CM can also promote skin rejuvenation because it is a rich source of growth factors, chemokines, and cytokines, including vascular endothelial growth factor, transforming growth factor-beta, interleukin-6, interleukin-8, and tumor necrosis factor-alpha, that have been shown to be upregulated during the inflammatory phase of the wound healing process.

"Although topically applied growth factors and cytokines can increase skin remodeling, their penetration into the skin may be limited because of their large molecular size. Skin microneedling prior to application of AF-MSC-CM creates a route for enhanced transdermal delivery," Dr. El-Domyati explains. "In contrast to use of embryonic stem cells, the AF-MSC-CM avoids ethical issues, has low immunogenic potential, and can be differentiated with a high degree of expansion and regeneration without culture."

STUDY RESULTS
The 10 study participants included three males and seven females, and they had a mean age of 50 years. Seven patients had Fitzpatrick skin type IV and three were Fitzpatrick skin type III. Facial aging at baseline based on the Glogau classification system was II or III.

Patients were assessed for adverse events at each visit. The only issues recorded were post-treatment erythema and edema that resolved within 1 to 2 days.

"Because microneedling creates only minute holes in the epidermis, it is associated with minimal to no risk of postinflammatory hyperpigmentation," Dr. El-Domyati says.

The assessments of clinical improvement from baseline were done by two blinded dermatologists who compared photographs obtained at baseline and one month after the last treatment. They rated changes on both sides of the face that included improvement in forehead wrinkles was observed, but to a lesser degree than wrinkles in the crow's feet area and in only 50% of patients," Dr. El-Domyati says.

Although they were not aware of which side of the face was treated with the AF-MC-CSM, patients were asked to rate their overall treatment satisfaction rather than separately for each side of the face. Six patients were "completely satisfied", two were "somewhat satisfied" and two were "unsatisfied."

Histological changes were assessed by comparing findings on pre- and post-treatment biopsies taken with a 3 mm punch probe from the temporal area. The histology showed positive changes on both sides of the face that included increased number and organization of collagen bundles, decreased interfibrillary spaces, decreased elastic material, and the development of fine and well-arranged elastic fibers. However, the changes were greater on the right side of the face.

Epidermal thickness was also measured and found to increase significantly from baseline on both the microneedling alone and combination treatment sides. The difference between the two sides was not statistically significant.

Disclosures:
Dr. El-Domyati has no relevant financial interests to disclose.

References:
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Watch the first episode here: crownlaboratories.com/microbiome
Pipeline agents to treat hematologic malignancy

LISETTE HILTON | Staff Correspondent

Researchers are learning more about how to diagnose and better treat blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare cancer that often presents with skin manifestations, according to a review published March 2020 in Current Opinion in Hematology.

BPDCN patients have suffered historically poor outcomes. Years ago, doctors were limited to treating these patients primarily with intensive chemotherapy regimens used to treat acute myeloid leukemia or acute lymphoblastic leukemia patients.

But in 2018, the U.S. Food and Drug Administration (FDA) approved tagraxofusp-erzs (Elzonris, Stemline). Tagraxofusp-erzs is the first approved drug indicated specifically for BPDCN, and its use is recommended in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.

Never targeted agents to treat the hematologic malignancy are in the pipeline.

NOTABLE CHANGES IN RECENT YEARS
The World Health Organization (WHO) named BPDCN and classified it under acute myeloid leukemia and related precursor neoplasms in 2008. Some eight years later, WHO established BPDCN as a distinct entity.

Just how many people have BPDCN isn’t clear. But it is thought that there are about 0.04 cases of the cancer per 100,000 people. And about three in four patients are older men.

Derived from plasmacytoid dendritic cells, BPDCN generally is an aggressive disease. It presents clinically on the skin in about nine out of every 10 cases with asymptomatic skin lesions that often appear as bruise-like lesions, plaques or nodules.

While a small percentage of patients will present with skin disease only, most show signs of BPDCN in the bone marrow, lymph nodes or visceral organs. Rarely, patients will have no cutaneous evidence and instead present with the leukemic phase of the cancer. About 30% of patients also have central nervous system involvement.

“Flow cytometry to determine the immunophenotype is an essential component of diagnosing [BPDCN],” the author writes.

CD123, an interleukin-3 receptor alpha, is over expressed in nearly all BPDCN cases. These cancer cells also may be positive for CD4, CD56, CD303 or FcL1, according to the paper.

Some authors have found a recurrent MYC gene rearrangement in these patients. That particular genetic aberration is associated with an older age at diagnosis and worse prognosis.

TREATMENT IS EVOLVING
Unfortunately, doctors have to rely largely on retrospective studies looking at BPDCN treatment options.

Those studies suggest that, generally, BPDCN responds better to acute lymphoblastic leukemia regimens compared to acute myeloid leukemia treatment options. However, most responses to these regimens are transient, the author reported.

Retrospective studies suggest allogeneic stem cell transplant for eligible patients in their first remission offers the highest overall survival rates, including three- and four-year overall survival rates ranging from 74% to 82%.

Tagraxofusp-erzs targets CD123. It consists of recombinant human interleukin(IL)-3 fused to a truncated diphtheria toxin, according to the paper.

“Binding the drug to CD123 on the cell surface leads to cellular internalization of the diphtheria toxin, which ultimately leads to inhibition of protein synthesis and cell death,” the author writes.

In a phase 1/2 clinical trial of 44 untreated or relapsed/refractory BPDCN patients, 21 of 29 previously untreated patients achieved complete remission and 13 of those went on to have a stem cell transplant. Overall response rate of the 15 patients with relapsed/refractory BPDCN was 67% with tagraxofusp-erzs, with an average overall survival of 8.5 months.

Eighteen of the 44 patients studied developed capillary leak syndrome. Two patients died from capillary leak syndrome during the study.

Researchers are studying investigational agents aimed at treating BPDCN. These include IMGN632, a humanized antibody-drug conjugate with an anti-CD123 monoclonal antibody conjugated to a DNA-alkylating payload, the author writes.

Researchers are evaluating the safety and efficacy of treating CD123-positive malignancies including BPDCN with the monoclonal antibody targeting CD123 and CD3 XmAb14045.

Venetoclax, a BCL-2 inhibitor, is yet another agent in the pipeline for BPDCN patients.

“... as knowledge is gained on the molecular changes that occur in [blastic plasmacytoid dendritic cell neoplasm], this will ideally lead to more targeted and effective therapies in the years to come,” the author writes.

Disclosure: Kendra Sweet, M.D., has received honoraria from Stemline Therapeutics.

Reference:
Patient volumes are rising, but still significantly lower than last year.

From Page 1

50%, second only to cardiology.¹

“We know that every patient is having a different experience and taking a different approach to in-office dermatology appointments, depending on their region, government regulations and personal comfort levels,” says Rhonda Peebles, vice president and head of U.S. Dermatology for UCB.

“One thing we can all agree on is that the normal rules of engagement are a thing of the past. And UCB is thinking through the lens of the future to anticipate what a post-pandemic world will look like for healthcare, so we can adjust our support strategies for clinicians and patients in an appropriate way,” Ms. Peebles adds.

When California’s shelter-in-place order began March 17, says Wendy Roberts, M.D., “Everything came to a screeching halt. People were canceling in droves.” She is a dermatologist and dermatopathologist in solo private practice in Rancho Mirage, Calif.

That afternoon, Dr. Roberts sent her patients a lengthy email.

“In times of crisis, you have to communicate with your patients — not your staff, you, the doctor,” she says.

She reassured patients, encouraging them to do what they felt comfortable with. She also told patients that, being essential per U.S. Centers for Disease Control guidelines, her medical practice would remain open.

That same day, she rearranged her 6,500-square-foot office. The new workflow starts with calling patients before their appointment to check their COVID-19 status and, once they arrive, whisking them from their cars to an exam room — without ever encountering another patient.

“There’s no reception. You come right into your room. We’re all in personal protective equipment (PPE) — me, the staff, everybody,” she says.

Post-visit, patients check out from their exam rooms and leave the practice via an exit-only door.

“Every person who walks through the door gets screened for temperature. They’re asked questions. No one is allowed in the building without a mask,” Dr. Friedman says.

Throughout the facility, signage shows patients where to wait for elevators and where to stand before the massive Plexiglas shields that guard each front desk.

TELEMEDICINE TO THE RESCUE

Equally important to dermatologists’ pandemic response was implementing telederm. Dr. Friedman says that riding out the pandemic has been “a bit of a roller coaster.” In response to waivers of governmental and insurers’ restrictions on telemedicine, however, his department quickly adopted the technology.

“Even though we were still able to have clinical productivity, it was a fraction of what we were pre-COVID,” he says. “But it revved up pretty fast. We were seeing hundreds, and then several thousand telehealth visits.”

Joel Schlessinger, M.D., says that through the end of April, his business was down easily 75%. He is an Omaha, Neb.-based board-certified dermatologist and cosmetic surgeon and CEO of LovelySkin. While his cosmetic practice shut down for three months, he swiftly began funneling nonurgent medical appointments to teledermatology.

“That allowed us to decrease the density of people in the office,” he says.

During the heart of the shutdown, he and two PAs saw a total of 50 telemedicine patients daily.

Dr. Schlessinger says that his medical and aesthetic practices have rebounded to varying degrees. Many existing and new patients are scheduling cosmetic procedures, he adds, after watching their faces on Zoom screens for countless hours.

Although his cosmetic business is growing month-by-month, cosmetic revenues remain significantly down versus 2019.

“If things continue as they are, we may come close to even by the end of the year,” he says. “We’re still running at about 75% to 80% of our maximum compared to pre-pandemic,” he adds.

This situation likely will persist at least until the pandemic is under control or a vaccine emerges, he says.¹

References:

Disclosures:
Dr. Roberts, Friedman and Schlessinger report no relevant financial interests. Ms. Peebles is an employee of UCB.
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