Comorbidities require robust dialogue

JOHN JESITUS | Staff Correspondent

Current joint psoriasis guidelines from the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) emphasize the need to help patients understand the relationship between psoriasis and comorbid conditions and the importance of seeking appropriate interventions as needed. Psoriasis carries a specific set of comorbidities, and dermatologists are often the first doctor to see these patients, says guidelines co-author Mark Lebwohl, M.D. Therefore, he says, a dermatologist must often be the person who triggers patients to visit their cardiologist, internist or rheumatologist, and so pay attention to their comorbidities. He is the Waldman Professor and Chairman, Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai.

ILYA PETROU, M.D. | Staff Correspondent

A new technology based on nano-pulse stimulation (NPS) appears to be effective for treating a growing list of benign dermatologic indications, and now it’s being investigated for nonmelanoma skin cancer, one expert says.

With potentially fewer side effects, this technology has definitive advantages over traditional modalities that may make it an excellent treatment alternative in the future, says E. Victor Ross, M.D., Scripps Clinic Carmel Valley, Laser & Cosmetic Dermatology, San Diego, Calif., who spoke during the ODAC meeting in Orlando.

“Nano-pulse stimulation is an exciting new technology that likely has only touched the surface of its potential therapeutic utility in dermatology,” he says. “Beyond its proven efficacy in benign dermatologic lesions, this technology could potentially also prove useful in the treatment of nonmelanoma skin cancer such as basal cell carcinoma.”

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

Recognition of patients with hereditary melanoma is important not only because these individuals require careful surveillance for future primary melanomas, but also because they may be predisposed to multiple other types of malignancies because of their genetic mutation, says Hensin Tsao, M.D., Ph.D., professor of dermatology and director, MGH Melanoma and Pigmented Lesion Center, Massachusetts General Hospital, Harvard Medical School, Boston.
Research moves forward

by MIKE HENNESSY, SR.

AS THE UNITED STATES begins to emerge from quarantine and practices begin to operate in line with the new norms of a post-COVID-19 society, many patients are reaching out for care they may have postponed. Research hasn’t stopped and new findings are informing better ways to manage patients with many inflammatory conditions.

Over the course of the past year and a half, the National Psoriasis Foundation and the American Academy of Dermatology have been releasing updated guidelines on the care of patients with psoriasis. One of the more recently released recommendations is aimed at comorbidities. As dermatologists are oftentimes the first physician to see patients with psoriasis, it’s important to be able to recognize signs of comorbid conditions and when to facilitate the patient connecting with other specialists. In our cover story this month, Dr. Mark Lebwohl, Waldman Professor and Chairman, Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, shares best practices based on these new guidelines for evaluating and managing these patients. In an effort to best manage patients with psoriasis and their comorbidities, researchers evaluated data from 60 clinical trials to offer a reference for comparing biologics with regard to efficacy and outcomes. The results were published in JAMA Dermatology and provide a tool to help individualize therapy for patients (page 37).

New research in acne and rosacea is providing a better understanding of the pathogenesis of this condition, leading to the possibility of new therapeutic targets (pages 20, 21). Comparisons of existing therapies in combination (page 17) and new combinations (page 18) provide physicians with expanded options for treatment.

Devices have been utilized in many conditions and as therapeutic development advances, they still play a role in conditions like acne (page 19) and nonmelanoma skin cancer (page 29).

Research is advancing care beyond mainstream conditions with efforts under way to improve treatment for patients with both hidradenitis suppurativa (page 49) and promising drugs to manage the wounds of patients with epidermolysis bullosa (page 47).

We hope this information supports and informs as you bring you move forward with your patient care. ◈

MIKE HENNESSY, SR., IS CHAIRMAN AND FOUNDER OF DERMATOLOGY TIMES’ PARENT COMPANY, MJHLIFESCIENTIFIC.
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Crohn’s disease
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MELANOMA
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Sterilized wraps turned face masks

Innovation amid pandemic uses medical waste to address healthcare challenge

by HEATHER ONORATI | Associate Editorial Director

A third year resident in the department of dermatology at the University of California, Irvine (UCI) has kicked off a passion project turning discarded sterilization wrap into face masks that, initially, will be used by much of the clinical and non-clinical staff at UCI with the hope of reserving the N95 masks for protection during aerosolized procedures and with patients who have tested positive for COVID-19.

Aditi Sharma, M.D., who says her passion lies at the intersection of medicine, innovation and public health, identified the potential of surgical wrap material in the development of masks, tested the material, compared materials and now has masks in development – all within a month.

Dr. Sharma completed her undergraduate studies in biomedical engineering and then worked at the National Institutes of Health under NIAID director Anthony Fauci, M.D., who now serves as the leading medical expert in the Trump administration for the COVID-19 pandemic efforts. During her tenure there, she researched agents of biological warfare and bioterrorism. With an interest in finding a way to apply this knowledge, she went to work at the World Health Organization in Geneva, Switzerland, focusing on increasing access of medical devices in a low-income resource setting.

Upon her return to medicine, and in looking for a way to incorporate these interests, she discovered through an article by University of Florida researchers that the material many hospitals use to wrap surgical instruments had a high particle filtration efficiency and; therefore, could have the potential to be used for face masks.

“It’s actually made from something called polypropylene which is the exact material used in N95,” Dr. Sharma says. This insight intrigued her, and in further exploring how the material is developed, she found that plastic material is melted down and blown out into thin fibers, which creates a mechanical filtration. It is then treated with an electrostatic innovation.
innovation

“I think that this whole project has really highlighted ... the necessity of the medical field to start thinking about how we can recycle and repurpose a lot of the materials that we are using in the hospital to reduce the waste that we’re producing.”

Aditi Sharma, M.D., University of California, Irvine

Sterilized wraps become face masks with high filter efficiency  
FROM PAGE 7

charge, which results in an electric filtration. This process is what makes the surgical wrap material and the N95 material so good for the purposes of filtration, she says. However, there was no data around the surgical wrap material’s filtration efficiency.

“It was just a hypothesis. So that’s where I came in. I started thinking about how can we actually quantify the filtration efficiency of this material,” Dr. Sharma says.

Dr. Sharma and colleague Melissa Chang, M.D., M.B.A., an anesthesiologist at UCI, decided to collect and compare potential materials.

They sent the Halyard H600 sterilization wrap by Halyard Health as well as Gemini sterilization wrap by Medline industries, both materials that are used by most hospitals and clinics around the world, for testing to Greg Rutledge, Ph.D., professor of chemical engineering at Massachusetts Institute of Technology, Cambridge, Mass.

What they discovered was that the Halyard material filtered up to 86.5% of particles, while the Gemini material filtered 73.5%. While not quite the standard the N95 masks offer, this is much higher than the filtration efficiency of mainstream masks that many individuals are currently making and wearing during this pandemic, which can vary in efficiency, but the cloth mask Dr. Sharma had tested filtered 26.1% of particles.

So, while not a substitution for the N95 mask, the filtration is much higher than masks made of more common household materials, she says and adds, “maybe this would be the universal mask that everybody in the hospital wears, from the custodial services to the people working in the cafeteria, to the healthcare workers. And then we really reserve those N95 and surgical masks for the procedures that they were designated to be used for.”

This insight drove the design of the first wave of 2,000 masks that are now being created with a community partner. The Halyard surgical wrap is being used as the base for the highest filtration efficiency; while the straps are being made with the Gemini material.

“The entire mask is recycled and recyclable,” she says.

Her hope is that these masks may help to address the shortage in hospitals, as well as make better use of materials that are often discarded anyway. During her research around the creation of these masks, she has found that 2,000 tons of medical waste is produced in the United States every day.

“I think that this whole project has really highlighted — at least for me — the necessity of the medical field to start thinking about how we can recycle and repurpose a lot of the materials that we are using in the hospital to reduce the waste that we’re producing, and especially when they can be used for something as productive and helpful as a mask,” Dr. Sharma says.

SURGICAL WRAP COLLECTION

Currently, the University of California, Irvine has developed a protocol for collecting the surgical wrap to then be used for the development of the first wave of masks. There is also a protocol for the use of the material once delivered to the seamstresses.

Dr. Sharma says she and colleagues are looking at making this a broader initiative as they’ve received interest from other universities both locally and nationally. The surgical wrap material is used globally, she says, so there is great potential.

For institutions that may be interested in collecting material for donation to this project, Dr. Sharma says they are using an internal material collection process that looks like this:

SPD PROCESS: After thorough instrument cleaning, please use caution when wrapping the instruments for sterilization. Minimize any extra sticker, label, or tape usage on the sterilization wrap. All of this tape must be cut around and the portions of this fabric that are taped over are unusable for the body of the mask.

OR PROCESS:

- All trays should be opened prior to patient entering room.
- These wraps will be placed in a clean bag and removed from the OR prior to the patient entering the OR.
- Any trays opened once the patient has entered the room would render those sterilization wraps no longer clean.
- The sterilization wraps should remain in the clean bags and should be accumulated in a designated area that is clean and away from patient care.
- These bags will be given to the seamstresses to start the sewing process.

As for sending the material to Dr. Sharma at UCI, this is a process in development with information to come soon. If you’d like to be notified when they are ready to receive materials, please message us at dermatologytimesmag@gmail.com. We’ll let you know! •
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In the COVID-19 era, this standard of care is still evolving.”

Do state guidelines overrule CDC?

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. Virus is ecstatic. He can, he hopes, quickly rebuild his medical and cosmetic dermatology practice. Although he had required that his staff use gloves and masks, and followed all CDC guidelines, all rules are now relaxed. He is comfortable moving forward and has been assured by his governor’s pro-business daily conferences. Hundreds of patients have returned to his office. As Dr. Virus reopens his office to its pre-corona status, one of his staff members becomes infected with the COVID-19. Within three weeks, almost 50 patients who had been seen in the office also become infected. Over the course of the next two months, eight patients end up on ventilators and three have died. Numerous patients file medical malpractice lawsuits against Dr. Virus. Although upset about all the illness, Dr. Virus feels comfortable with his decisions because he followed his governor’s guidelines. However, the crux of the medical malpractice lawsuit is that he did not follow CDC guidelines. Who wins? Should Dr. Virus mismanaged the case and that the negligence led to damage of the patient, then the physician will be liable. Conversely, if the jury believes an expert for the defendant doctor, then the standard of care, in that particular case has been met. In this view, the standard of care is a pragmatic concept, decided case-by-case, based on the testimony of physician.

It is important to note that where there are two or more recognized approaches of dealing with a situation (in this case the governor’s executive orders vs. CDC guidelines), a physician does not fall below the standard of care by using any of the acceptable methods even if one method leads to a higher incidence of problems than another.

Finally, in many jurisdictions, an unfavorable result due to an “error in judgment” by a physician is not in and of itself a violation of the standard of care if the physician acted appropriately prior to exercising his professional judgment. The standard of care is simply the way in which the majority of the physicians in a similar medical community would practice. If, in fact, the expert himself does not practice like the majority of other physicians, then the expert will have a difficult time explaining why the majority of other physicians practice differently. It would seem then that, in the perfect world, the standard of care in every case would be a clearly definable level of care agreed on by all physicians and patients. Certainly, in the COVID-19 era, this standard of care is still evolving. Unfortunately, with all suggested guidelines, there will be illness and there will ultimately be lawsuits. Time will tell.
How do phone apps for facial appearance work?
There seems to be an app for everything: losing weight, measuring hair loss, and facial appearance. The apps appear to be highly sophisticated and are very popular with consumers, but how do they work?

The facial appearance apps work by allowing consumers to download and use the software for free. The phone images taken by the consumer using the app become part of a database. Consumers answer several questions including age, sex, ethnicity, skin color, eye color, sun exposure history, etc. These answers and their images are stored by the app developers to construct a database that can be used to create overall skin health assessments, as well as an evaluation of spots, lines, wrinkles, and dark circles.

Each new user enriches and improves the image analysis capabilities of the app. Individual user images are compared to the database to allow a numerical score to be applied to the skin appearance characteristics of other individuals of the same, younger, or older age. These scores are then put into an algorithm to provide an apparent age assessment, which may elate or depress the user.

Are these phone apps accurate?
The accuracy of the apps depends on the expectations of the consumer. Adolescents are always happy if they look older, however mature individuals are always happy when they look younger than their chronological age. Problems with phone apps arise when expectations are not met.

One problem dermatologists may encounter is the patient who undergoes toxin and filler injections for appearance improvement and then uses her phone app to assess the results of her investment. Her phone app says she looks three years older after treatment than before. She returns to her physician’s office in tears stating the results of her treatment have been substandard and she demands her money back. Is it possible that she actually looks three years older? Should you return her money?

How can phone apps be influenced?
No, you do not need to refund her money, but it would be worthwhile to point out how phone apps can be manipulated. I performed a study on the effect of lighting on phone app results. We enrolled 60 female subjects Fitzpatrick skin types I-IV age 25-45 years. Higher Fitzpatrick skin types were excluded from the research because phone app companies state their apps are inaccurate for deeply pigmented skin. Reproducibly, patients looked three years younger under incandescent lighting than fluorescent/LED lighting.

Better lighting also minimizes the shadows of lines and wrinkles. You can easily demonstrate this phone app effect in your office for the patient. It is important to remember that the purpose of appearance assessing phone apps is not to provide an accurate assessment of consumer age, but rather to function as a targeted in-home portal for cosmetic and skincare product sales!
HUMIRA is the only FDA-approved treatment for your HS patients¹⁻³

Results Your HS Patients Can See

**MODERATE/STAGE II**
Actual HUMIRA-treated patient achieving HiSCR

Before

After

Photos courtesy of Dr. Marc Bourcier

HiSCR is at least a 50% reduction in total abscess and inflammatory nodule count, with no increase in abscesses and draining fistulas relative to baseline¹

**Indication¹**
**Hidradenitis Suppurativa:** HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older.

**Safety Considerations¹**
**Serious Infections:** Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immnosuppressants such as methotrexate or corticosteroids.

**Malignancies:** Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.
Clinically Meaningful Improvement (HiSCR) at Week 12

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

HUMIRA also has flare data available for HS

OCCURRENCE OF FLARE THROUGH 3 MONTHS
Pre-specified Other Secondary Endpoint in Period A

- 88% of patients on HUMIRA experienced no flares
- 65% control

HUMIRA-treated patients
n=316 for HUMIRA EW

Control patients
n=317 for control

PIONEER I (N=307) and II (N=326) were 36-week, randomized, double-blind, placebo-controlled clinical trials in adult patients with moderate to severe HS on HUMIRA 40-mg weekly (after initial doses).

22% (of 100) patients who were withdrawn from HUMIRA after 12 weeks experienced flare.

PIONEER I control=placebo.
PIONEER II control=placebo +/- antibiotic.

Integrated analysis of PIONEER I and PIONEER II through 12 weeks

Flare: ≥25% increase in AN count and an absolute increase of ≥2 relative to baseline

DATA LIMITATIONS

- Since PIONEER I did not reach statistical significance at the first key secondary endpoint, all endpoints in this integrated analysis cannot be regarded as statistically significant.

Safety Considerations (cont’d)

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the third page of this advertisement.

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To learn more, please go to ResultsforHS.com
IMPORTANT SAFETY INFORMATION for HUMIRA® (adalimumab)

SERIOUS INFECTIONS
Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. Reported infections include:

• Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.

• Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomyces, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.

• Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

• Do not start HUMIRA during an active infection, including localized infections.

• Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.

• If an infection develops, monitor carefully and initiate appropriate therapy.

• Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.
HEMATOLOGIC REACTIONS
• There is a known association between intermediate uveitis and central nervous system disorders that may lead to hospitalization or death in adult patients with rheumatoid arthritis (RA) who are treated with TNF blockers, including HUMIRA.

Infectious Diseases
HUMIRA is a biological medication that may alter the immune system's response to infections. While most patients receiving HUMIRA have not experienced serious infections, some have. Serious infections that may occur with the use of TNF blockers include tuberculosis (TB) and listeriosis.

TB
HUMIRA treatment is associated with an increased risk of reactivation of latent TB in patients who have had TB in the past. Consequently, patients with a history of TB should be evaluated carefully before treatment and treated appropriately.

Listeriosis
Listeriosis is a foodborne illness caused by the bacterium Listeria monocytogenes. It is associated with the consumption of unpasteurized dairy products and raw or undercooked meats, particularly processed meats. It can cause serious infection in some patients and is more common in immunocompromised individuals, including those receiving TNF blockers.

Other Serious Infections
HUMIRA has been associated with an increased risk of serious infections, such as pneumocystis pneumonia, histoplasmosis, coccidioidomycosis, and aspergillosis. Patients with severe infections should be evaluated and treated appropriately.

Clinical Trials Experience
In adult patients with chronic obstructive pulmonary disease (COPD), HUMIRA was associated with an increased risk of serious infections compared to placebo.

Recombinant Human Immunodeficiency Virus
In patients with HIV infection, the use of TNF blockers, including HUMIRA, is generally discouraged due to the risk of reactivation of latent HIV.

Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis, have been observed in patients treated with HUMIRA. Patients should be monitored for signs of anaphylaxis and treated appropriately.

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and IBD, the rate of serious infections was 2.2%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with Ps, the rate ofserious infections was 3.1%. However, due to the lower exposure to HUMIRA in patients with Ps, the rate of serious infections was not considered statistically significant.

In patients with AS, the rate of serious infections was 1.1%. HUMIRA-treated patients were less likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with CD, the rate of serious infections was 1.4%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with UC, the rate of serious infections was 1.0%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with IBD, the rate of serious infections was 1.0%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with Crohn's disease, the rate of serious infections was 1.5%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with ulcerative colitis, the rate of serious infections was 0.7%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with juvenile idiopathic arthritis (JIA), the rate of serious infections was 0.9%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with juvenile dermatitis and eczema, the rate of serious infections was 0.9%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of patients. In this population, the rate of serious infections was 1.2%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with polyarticular JIA who were <4 years of age, adalimumab antibodies were identified in 18% of patients. In this population, the rate of serious infections was 1.4%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with polyarticular JIA who were <4 years of age, adalimumab antibodies were identified in 18% of patients. In this population, the rate of serious infections was 1.4%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with systemic JIA who were <4 years of age, adalimumab antibodies were identified in 21% of patients. In this population, the rate of serious infections was 1.6%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

In patients with polyarticular JIA who were <4 years of age, adalimumab antibodies were identified in 18% of patients. In this population, the rate of serious infections was 1.4%. HUMIRA-treated patients were more likely to be taking concomitant immunosuppressants such as methotrexate or corticosteroids.

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Juvenile Idiopathic Arthritis Clinical Studies

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included 5%, respectively).

PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease was similar to the safety profile seen in patients with RA.

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in long-term follow up studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA.

The safety profile for patients with PsA treated with HUMIRA was similar to the safety profile seen in patients with RA.

HUMIRA has been studied in 1,696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in patients with RA. When treating patients with Ps, consideration should be given to the possibility of overlap with concomitant psoriatic arthritis.

HUMIRA has been studied in approximately 5,200 patients with ankylosing spondylitis (AS) in 14 placebo-controlled trials and in long-term follow up studies. The safety profile for patients with AS treated with HUMIRA was similar to the safety profile seen in patients with RA.

Ulcerative Colitis Clinical Studies

In Study UCD-I, the safety profile for subjects with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

The safety profile for subjects with UC treated with HUMIRA was considered consistent with the safety profile seen in patients with RA.

The safety profile for subjects with UC treated with HUMIRA was consistent with the safety profile seen in patients with RA.

Clinical Uveitis Clinical Studies

Safety Clinical Studies

Clinical IBD Clinical Studies

HUMIRA has been studied in 4,842 adult patients with RA and 1,678 adult patients with Ps with RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in patients with PsA.

HUMIRA has been studied in 1,300 patients with RA and 500 patients with Ps with RA and PsA. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in patients with PsA.

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Topical combo outperforms oral

LISETTE HILTON | Staff Correspondent

The topical combination of tretinoin 0.05% lotion (Altreno, OrthoDermatologics) and azelaic acid 15% foam improved truncal acne and may be an alternative to oral antibiotic treatment, according to case series of four acne patients published recently in Case Reports in Dermatological Medicine.1

About half of all facial acne patients have truncal acne. Dermatologists often treat truncal acne with oral antibiotics, sometimes due to anticipated challenges of applying a topical to a large body surface area. The problem is even in cases of severe inflammatory and nodular acne vulgaris, patients should take antibiotics for the short-term. And antibiotics can lead to other issues, from microbial resistance to gastrointestinal microbe disruption.

“In many cases of mild, moderate, or even severe truncal acne, combinations of topical therapies may be valid alternatives,” the authors wrote. “The introduction of foam formulations with enhanced percutaneous absorption and tretinoin lotion formulations that incorporate moisturizing/hydrating agents challenges the previously held idea that effective and tolerable treatment of truncal acne requires oral treatment.”

The authors reported outcomes from treating four female adult African-American truncal acne patients with a combination of tretinoin lotion 0.05% and azelaic acid foam. Each experienced sustained improvement of up to about three months using the topical combination. And each had tried other commonly used therapies, including antibiotics, with mixed results.

Patient one, a 30-year-old with a three-year history of severe back acne, was concerned not only about the acne but also the dark spots the lesions left behind. A dermatologist had prescribedoral erythromycin, which improved but didn’t clear her skin. The previous dermatologist then switched to oral doxycycline and adjuvant daily adapalene lotion 0.1%, which didn’t help. The author prescribed tretinoin lotion 0.05% for its favorable particle size, homogenous distribution and formulation. Tretinoin lotion 0.05% has added hyaluronic acid and collagen, which might decrease dryness and irritation, according to the paper. Azelaic acid foam, which the author prescribed twice daily, is known to have a lightening effect on skin.

At four weeks, the patient said she was satisfied with treatment and her dark spots appeared lighter. At 12 weeks, the author reported no evidence of acne and sustained post-inflammatory hyperpigmentation improvement.

Patient two, a 33-year-old with a long history of acne, seborrheic dermatitis and mild atopic dermatitis, tried many over-the-counter and prescription acne medications. Among the regimens she had tried for truncal acne: once daily oral doxycycline 150 mg and azelaic acid foam 15% twice daily. The patient said this and other regimens helped but didn’t clear her skin or the hyperpigmentation on her chest, shoulders and back.

Another regimen, which controlled her truncal acne for more than six months until the acne recurred, included benzofoam 9.8% topical foaming short contact cleanser for her face and chest, azelaic acid 15% foam for her chest, hydroquinone 4% lotion for the hyperpigmentation on her chest and back, as well as some facial treatment options. Three months into that regimen, she stopped taking oral antibiotics and began applying adapalene 0.1% lotion on the chest and back once daily.

The patient became frustrated with the hyperpigmentation on her chest, shoulders and back. Even a series of five chemical peels consisting of 20% salicylic acid effectively lightened the pigment and controlled the acne only initially.

Combination therapy with tretinoin lotion 0.05% twice daily and azelaic acid 15% foam controlled the truncal acne and post-inflammatory hyperpigmentation at four and eight weeks.

Patient three, a 24-year-old with long-term facial acne, complained of a recent severe flare of her acne on her neck, jawline and chest. Her neck had scarring, acne cysts, erythematous macules and hyperpigmented macules. Her chest had erythematous papules and macules and her back and shoulders had numerous erythematous papules and hyperpigmented macules. The authors wrote. The patient applied the tretinoin 0.05% lotion nightly to the chest, neck, shoulders and back and azelaic acid 15% foam twice daily to the chest, shoulders and back. The regimen also included medications to address the facial acne. At one month, her face, chest and neck were clear.

Patient four, a 32-year old with long-term facial acne, noticed truncal acne eruptions on her chest and back after she started working out.

The authors acknowledge the study’s relatively short follow-up is a limitation.
Quick Takes

Researchers have reported positive acne treatment outcomes with combining glycolic acid and salicylic acid in a solution for a superficial chemical peel. In a new study, more than 90% of patients reported decreased comedonal acne and cystic acne at two-week follow-up. Benzoyl peroxide and antibiotic treatments carry side effects; serum appears safe, effective for all skin types, ages.

Glycolic-salicylic acid serum safe, effective

LISETTE HILTON | Staff Correspondent

The authors of a recently published commentary report they’ve developed a glycolic and salicylic acid combination serum they say could disrupt traditional use of topical benzoyl peroxide and antibiotics to treat acne.

“Many companies capitalized on treatable skin conditions by providing expensive prescription medications or high-end over-the-counter cosmetics. However, patients have become more appreciative toward these medications in lieu of their often-detrimental side effect profile and reactivity with sensitive skin,” according to the authors of a recently published commentary report they’ve developed a glycolic and salicylic acid combination serum they say could disrupt traditional use of topical benzoyl peroxide and antibiotics to treat acne.

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“We recommend the use of the serum to patients with mild-to-moderate inflammatory and cystic acne, melasma, oily skin types, keratosis pilaris, seborrhea dermatitis, pseudo-folliculitis barbae, folliculitis, and rosacea.”

David Wiegmann, M.D.
William Beaumont Hospital-Royal Oak, Royal Oak, Mich.
Lori Haddad, D.O.
dermatologist, Birmingham, Mich.

At their two-week follow-up appointments, patients filled out a questionnaire reporting the skin changes they noted with treatment.

The authors found that more than 90% reported decreased comedonal acne and cystic acne; about 80% reported decrease oil production; and about 70% noted fading hyperpigmentation. Nearly 80% said their skin tone improved; more than 90% reported improved skin texture; and about 90% noted an overall improvement in their acne.

Findings from their physical examinations were similar to what patients reported, according to the paper.

“One patient stopped using the serum after one week because of itchiness, according to the paper.

Acne medications with benzoyl peroxide and antibiotics have dominated acne treatments, according to the authors. But both come with side effects. For example, benzoyl peroxide can cause hypopigmentation and isn’t safe for darker skin types.

“Today’s patients want a more natural, safer approach for treating their skin. Glycolic and salicylic acids are well-known peeling agents used to treat melasma and acne and work synergistically in the topical serum, according to the authors.

“In addition, it is safe in all ethnicities, all ages, male and female and safe during pregnancy. The formula is ‘organic’ and is allergy-free, dye-free, ethonalamine-free, paraben-free, propylene glycol-free, and sulfate-free,” they wrote. “We recommend the use of the serum to patients with mild-to-moderate inflammatory and cystic acne, melasma, oily skin types, keratosis pilaris, seboreea dermatitis, pseudo-folliculitis barbae, folliculitis, and rosacea.”

Reference:
1. Wiegmann, D, Haddad, L. Two is better than one: The combined effects of glycolic and salicylic acid on acne-related disorders. J Cosmet Dermatol. 2020;00: 1-3.

Disclosures:
The authors developed the serum studied.
Utility of lasers in acne Tx

ILYA PETROU, M.D. | Staff Correspondent

The popularity of laser and light devices has recently grown among acne patients, not only due to their efficacy but also because treatments are quick and clean, says Michael H. Gold, M.D., director, Gold Skin Care Center, Tennessee Clinical Research Center and The Laser and Rejuvenation Center, and Clinical Assistant Professor of Dermatology at Vanderbilt University School of Medicine and School of Nursing, Nashville, Tenn.

“T
he interest in laser and light modalities has gotten much greater over recent years as we learn more about how these devices work and how they can fit in our treatment protocols, particularly with all the current concerns over antibiotic resistance, patient compliance with medicines, medicines that can take too long to work and are perhaps too expensive or not covered by insurances,” he says. Dr. Gold shared insights with colleagues during the 18th Annual South Beach Symposium, Miami, Fla.

There are several different laser and light devices that are currently used and work very well in acne treatment. Among them, blue light remains one of the oldest modalities that, historically, has achieved excellent reproducible outcomes. The modality has approval from the U.S. Food and Drug Administration (FDA) to treat up to severe cases of acne and, according to Dr. Gold, physicians should not discard blue light as ‘old technology,’ but, instead, recall its significant utility in quelling symptoms.

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Therapeutic options to improve management

ILYA PETROU, M.D. | Staff Correspondent

As the pathogenesis of rosacea is still largely unclear, physicians often grapple with finding an optimal treatment and management plan. However, continued research has highlighted neuroinflammation and neurogenic inflammation as important contributing factors in the development of the skin condition, and insights like these have lead to improvements in therapeutic management.

Rosacea occurs in approximately 10% of individuals usually after the fourth decade of life and is diagnosed in over 13 million patients in the United States alone. The condition often carries implications far beyond the skin and can take a significant toll on a patient’s psyche and general well-being.

The condition is characterized by a mosaic of symptoms, including facial erythema and telangiectasias, papules and pustules, as well as facial edema, typically occurring on the central face around the nose, cheeks, forehead and chin. According to the presentation of symptoms, it can be further divided into four subtypes including erythematotelangiectatic rosacea (erythema, flushing, telangiectasias), papulopustular rosacea (erythema, edema, acne-like lesions), phymatous rosacea (rhinophymatous changes), and ocular rosacea, which can cause significant inflammation leading to dryness, redness and irritation of the eyes, resulting in transient vision changes and even permanent vision damage after persistent chronic inflammation of the cornea.

"The current pathophysiological model of rosacea implicates an upregulated, dysregulated innate immune system prone to excessive inflammation and vasodilation coupled with neurogenic dysregulation and extrinsic triggers and exacerbating factors." Justin W. Marson, M.D., and colleagues University of California, Irvine, Orange, Calif.

Recent data sheds light on the pathogenesis of rosacea and outlines treatment options to better manage patients. Hyperactive neurovasculature appears to be one of the keys in developing symptoms. Dysregulated innate and adaptive immunity also play a central role.

Recent data sheds light on the pathogenesis of rosacea and outlines treatment options to better manage patients. The microbiome has also been thought to instigate and propagate a dysfunctional immune system and, of the several suspected cutaneous microbes, demodex folliculorum (and its native microbe Bacillus oleronius) has most notably been implicated in the inflammatory response in rosacea. Past studies have shown Demodex density to be higher in areas of rosacea compared with healthy skin in the same patient, and almost six times higher in patients with rosacea compared with healthy subjects.

The conventional wisdom for rosacea is that the innate immune system cannot appropriately recognize the commensal organisms that live and breed naturally on the skin such as C. acnes, S. epidermidis, and, perhaps, Demodex. The result is an inflammatory response to these organisms by the innate immune system, translating clinically into rosacea. Moreover, the authors state that patients with rosacea may have an altered gastrointestinal microbiome that can contribute to their disease symptoms, which can be associated with gastrointestinal disorders, including celiac disease, Crohn’s disease, ulcerative coli-
Skin microbiota, comorbidities linked

ILYA PETROU, M.D. | Staff Correspondent

It has become increasingly clear that rosacea is not just a cutaneous disease with local implications but instead, part of a still largely obscure and complex systemic inflammatory disease process. A recent paper found that the skin’s microbiota is closely associated with a number of systemic diseases, underscoring the need for clinicians to not only address the microbiota but also consider appropriate antibiotic therapy when contemplating treatment in rosacea patients.

“From our past work, we’ve consistently seen a very strong link between rosacea and various systemic disorders, and what always came out from our analyses was that the GI comorbidities showed a clear-cut connection to rosacea,” says Anna Lien-Lun Chien, M.D., associate professor of dermatology and co-director of the cutaneous translational research program, department of dermatology, Johns Hopkins University, Baltimore, and co-author of the paper. “This is what led us to explore the role of the skin’s microbiota as a possible pathogenesis and common denominator between rosacea and systemic diseases.”

Dr. Chien and colleagues investigated the skin’s microbiome as it relates to the types and severity of rosacea. The researchers found that the bacteria environment of the skin in rosacea patients is very different from that in healthy skin. Some bacteria species were very abundant that are not typically seen in uninvolved healthy skin Dr. Chien says, and there were some bacteria that were very much reduced.

“We found the Campylobacter bacteria to be very much abundant in patients with rosacea. Interestingly, the same bacteria have also been implicated many times in the gut microbiome in patients with ulcerative colitis and other GI diseases. Perhaps this indicates a similar pathogenesis and explains why we often see GI diseases in rosacea,” Dr. Chien says.

Prevotella bacteria, which has been linked to cardiovascular conditions including atherosclerosis, were also found to be increased in the microbiome of rosacea skin. This may contribute to the increased association of cardiovascular disorders in rosacea patients. Past reports have shown that Acinetobacter bacteria help patients with atopic dermatitis and those with allergic and atopic tendencies. Interestingly, Acinetobacter bacteria were found to be very low in skin of rosacea patients, which according to Dr. Chien, may explain why allergic diseases tend to be more commonly seen in rosacea patients.

“We’ve consistently seen a very strong link between rosacea and various systemic disorders and what always came out from our analyses was that the GI comorbidities showed a clear-cut connection to rosacea.”

Anna Lien-Lun Chien, M.D. Johns Hopkins University, Baltimore

“We found a tremendous amount of interesting data, which opens the door for many potential shared pathologic pathways between rosacea and systemic illnesses. We definitely can’t think of rosacea as a skin only disease anymore, especially with its increasingly clearer links to the microbiome and the associated systemic inflammatory diseases,” Dr. Chien says.

According to Dr. Chien, dermatologists should actively ask their rosacea patients about their medical history, especially GI complaints, the medicines they are taking, and if they follow with a primary care physician.

Rosacea patients should be assessed if they exhibit any non-cutaneous symptoms and should seek appropriate specialist according to their symptoms.

Past studies have demonstrated that antibiotics can exacerbate some of the GI symptoms associated with rosacea and certain types of antibiotics have an even greater link to some of these GI associations. According to Dr. Chien, rosacea patients have a tendency for GI diseases and antibiotics may further exacerbate these illnesses.

Antibiotic stewardship is crucial Dr. Chien says, and while clinicians need antibiotics for rosacea, acne and many other skin conditions, it is very important to remain responsible when prescribing them to patients.

“We have seen a tremendous amount of interest data, which opens the door for many potential shared pathologic pathways between rosacea and systemic illnesses. We definitely can’t think of rosacea as a skin only disease anymore.”

Disclosures:
Dr. Chien reports no relevant disclosures.
In designing a therapeutic approach ... ask the patient of their perception of disease severity and what about the disease process concerns them most.”

Justin W. Marson, M.D., and colleagues, University of California, Irvine, Orange, Calif.

The therapeutic options advance on new understandings from page 20

LEO PHARMA MAKES AZELAIC ACID FOAM AVAILABLE

By MORGAN PETRONELLI

LEO PHARMA ANNOUNCED APRIL 15 that they are bringing azelaic acid foam 15% (Finacea, LEO Pharma) back to the market.

Azelaiac acid foam 15% is available by prescription to treat the inflammatory pustules and papules of mild-to-moderate rosacea.

Leo Pharma acquired the brand in the company’s acquisition of Bayer’s prescription dermatology business in 2018. Following the acquisition, production of the prescription treatment was suspended due to a manufacturing delay in mid-2019. The company says they have located the problem and production of the product will now continue, according to the press release.

“We are pleased to bring Finacea Foam back on the market as an option for healthcare providers and their patients in the treatment and management of mild-to-moderate rosacea,” says Christopher Ronner, president and CEO of LEO Pharma Inc. “People affected by rosacea are challenged by a chronic condition that affects the face, with symptoms including raised spots and pimple-like bumps. Helping patients is our mission at LEO Pharma, and we remain committed to supporting the medical dermatology community.”

Some of the most common side effects when using the foam are itching, redness, dryness and pain (tender-ness, stinging or burning). Additionally, there have been isolated occurrences of hypopigmentation after some people have used azelaic acid.

References:


In rosacea and inflammatory bowel syndrome, as well as other systemic inflammatory diseases.

“In designing a therapeutic approach, it is also important for physicians to not only determine severity but also ask the patient of their perception of disease severity and what about the disease process concerns them the most. These two principles, in turn, can help guide development of the therapeutic regimen,” the authors write.

Appropriate skin hygiene as well as lifestyle modifications that include avoiding the potential precipitating and exacerbating factors of rosacea can help mitigate disease severity. According to the authors, patients should be encouraged to avoid chemical or physical exfoliants and alcohol-based topical products, use moisturizers, wash their face with mild, synthetic detergent-based products, as well as apply sunscreens with an SPF 30 or greater that can provide broad-spectrum UV and visible light protection.

A number of topical preparations can be used to help address the persistent erythema, telangiectasias and flushing including brimonidine 0.33% gel, an alpha-2 adrenergic agonist, and oxymetazoline 1% cream, an alpha-1 adrenergic agonist, both aimed at constricting facial blood vessels. Laser and light therapies including the pulsed dye (PDL) and potassium-titanyl-phosphate (KTP) lasers as well as intense-pulsed light (IPL) have also demonstrated efficacy in diminishing erythema and some degree of flushing, removing telangiectasias and improving quality of life.

A range of first-line topical and oral agents are currently being used to treat the papules and pustules in rosacea including topical tetracyclines 1% cream, azelaic acid 15%, and metronidazole 0.75% gel, cream or lotion. Other agents that have also proven effective include clindamycin 1% gel with and without 5% benzoyl peroxide, erythromycin, minocycline, permethrin and topical retinoids. In more severe cases, varying combinations of topical and oral medications are also employed.

Isotretinoin as well as the systemic antimicrobial and anti-inflammatory agents used for papulopustular rosacea can also work well in the early active inflammatory stages of phymatous rosacea, while advanced disease hallmarked by hypertrophy and nodular growths may be best addressed with procedural techniques including ablative CO2 or erbium laser, radiofrequency or surgical debulking.

According to the authors, ocular rosacea can occur in approximately half of patients with cutaneous rosacea, may precede cutaneous symptoms in 20% of patients, or can develop independently. Here, first-line treatments include topical azithromycin and calcineurin inhibitors used alone or in combination, while more severe ocular symptoms can be treated with oral azithromycin, anti-inflammatory dose doxycycline, as well as other tetracyclines.

“Most patients with rosacea present with combination disease of papules, telangiectasias, erythema and pustules. Successful treatment of rosacea patients requires ascertaining what aspects of their disease are most troublesome to them and devising a multi-therapy approach to address all clinical findings,” the authors write.

Disclosure:

Dr. Marson reports no relevant disclosures.

References:


An experience worth noticing.

With clinical efficacy and safety profile in a once-daily spray foam, choose the Enstilar® Foam experience for your patients with plaque psoriasis.¹

In adults, patients achieved “Clear” or “Almost Clear” skin as measured by IGA¹,²:

- 53.3% vs 4.8% for vehicle at Week 4 (P<0.001)
- 26.4% vs 1.9% for vehicle at Week 2

¹Valid for up to 12 prescription fills per calendar year. Patients are not eligible if they are enrolled in or eligible for any state or federally funded health care program (e.g., Medicare, Medicaid). Additional restrictions and limitations apply; see www.leopharmaconnect.com.

²A randomized clinical trial with 426 patients, ≥18 years of age, that investigated the effectiveness of Enstilar® or the vehicle alone for the treatment of psoriasis vulgaris on the trunk and/or limbs. Efficacy was assessed using a 5-point IGA at Week 4, with treatment success defined as the percentage of patients who achieved at least a 2-step improvement to reach “Clear” or “Almost Clear” disease severity. Patients with “Mild” disease were required to be “Clear” to be considered a treatment success.¹,²

IGA=Investigator’s Global Assessment.

Not an actual patient. Image is a representation of plaque psoriasis. Individual results may vary.


INDICATION AND USAGE

Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Discontinue use when control is achieved. Instruct patients not to use more than 60 grams every 4 days.

IMPORTANT SAFETY INFORMATION

For topical use only. Enstilar Foam is not for oral, ophthalmic or intravaginal use and should not be applied on the face, groin or axillae or if skin atrophy is present at the treatment site. Do not use with occlusive dressings. Patients should wash hands after application.

Please see Brief Summary of Prescribing Information on following page.
BRIEF SUMMARY OF PRESCRIBING INFORMATION.

INDICATIONS AND USAGE
Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 12 years and older.

DOSEAGE AND ADMINISTRATION
Instruct patients to shake can prior to using Enstilar Foam and to wash their hands after applying the product. Apply Enstilar Foam to affected areas once daily for up to 4 weeks. Rub in Enstilar Foam gently. Discontinue Enstilar Foam when control is achieved. Patients should not use more than 60 grams every 4 days.

Enstilar Foam should not:
• Used with occlusive dressings unless directed by a healthcare provider.
• Used on the face, groin, or armpit, or if skin atrophy is present at the treatment site.

Enstilar Foam is not for oral, ophthalmic, or intravaginal use.

DOSE FORMS AND STRENGTHS
Enstilar Foam: 0.005%/0.064% - each gram contains 50 mcg calcipotriene and 0.643 mg of betamethasone dipropionate in a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Flammability
The propellants in Enstilar Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Hypercalcemia and Hypercalciciuria
Hypercalcemia and hypercalciciuria have been observed with use of Enstilar Foam. If hypercalcemia or hypercalciciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciciuria following Enstilar Foam treatment of more than 4 weeks has not been evaluated.

Effects on Endocrine System
Hypothalamic-Pituitary-Adrenal Axis Suppression
Systemic absorption of topical corticosteroids can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. If HPA axis suppression is documented, gradually withdraw Enstilar Foam, reduce the frequency of application, or substitute with a less potent corticosteroid.

The following trials evaluated the effects of Enstilar Foam on HPA axis suppression:
• In a trial evaluating the effects of Enstilar Foam on the HPA axis, 35 adult subjects applied Enstilar Foam on the body and scalp. Adrenal suppression was not observed in any subjects after 4 weeks of treatment. In another trial, 33 pediatric subjects aged 12 to 17 years applied Enstilar Foam on the body and scalp. Adrenal suppression occurred in 3 (9%) of the subjects.

Cushing’s Syndrome and Hypercorticism
Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hypercorticism, and glucauria.

Additional Considerations for Endocrine Adverse Reactions
Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Allergic Contact Dermatitis
Allergic contact dermatitis has been observed with topical calcipotriene and topical betamethasone. Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Corroboration such an observation with appropriate diagnostic patch testing.

Ophthalmic Adverse Reactions
Use of topical corticosteroids, including Enstilar® Foam, may increase the risk of posterior subcapsular cataracts and glaucoma and have been reported with the postmarketing use of topical corticosteroid products. Avoid contact with Enstilar Foam with eyes. Enstilar Foam may cause eye irritation. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

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.

Clinical Trials Conducted in Subjects 18 years and older with Psoriasis
The rates of adverse reactions described below were from three randomized, multicenter, vehicle-placebo-controlled clinicial trials in adult subjects with plaque psoriasis.

Subjects applied study product once daily for 4 weeks, and the median weekly dose of Enstilar Foam was 25 grams. Adverse reactions reported in <1% of adult subjects treated with Enstilar Foam included; application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis.

Clinical Trials Conducted in Subjects 12 to 17 years with Psoriasis
In an uncontrolled clinical trial, 706 subjects aged 12 to 17 years with plaque psoriasis of the scalp and body applied Enstilar Foam once daily for up to 4 weeks. The median weekly dose was 40 grams. Adverse reactions reported in <1% of pediatric subjects treated were acne, erythema, application site pain, and skin reactions.

Postmarketing Experience
Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids included atrophy, striae, telangiectasias, dryness, perioral dermatitis, secondary infection, and miliaria.

Ophthalmic adverse reactions of cataracts, glaucoma, increased intraocular pressure, and central serous chorioretinopathy have been reported with the use of topical corticosteroids, including topical betamethasone products.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Available data with Enstilar Foam are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene after topical administration of Enstilar Foam is likely to be low.

Observational studies suggest an increased risk of having low birth weight infants with the maternal use of potent or super potent topical corticosteroids. Advise pregnant women that Enstilar Foam may increase the potential risk of having a low birth weight infant and to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail). The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of Enstilar® Foam.

The estimated background risk of major birth defects and miscarriage of 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% to 4% and 15% to 20%, respectively.

Data
Human Data
Available observational studies in pregnant women did not identify a drug-associated risk for major birth defects, preterm delivery, or fetal mortality. The use of topical corticosteroids of any potency. However, when the dispensed amount of potent or super potent topical corticosteroids exceeded 300 grams during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data
Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m2/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight, or effects on litter parameters, and no effects on the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 mcg/kg/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs. Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m2/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day; reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternebrae, pubic bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2000 mcg/kg/day (0, 468, 1875, and 7500 mcg/m2/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternebrae). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at dosages of 0, 0.625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/kg/day, respectively) on days 6 through 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations (including absence of phalanges of the first digit and cranial dysplasia) at dosages of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and postnatal development when orally administered to pregnant rabbits at dosages of 0, 6, 18, or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m2/day, respectively) from day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.
Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (9, 600, 1800, and 6000 mcg/m²/day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring to reproduce was not affected.

Lactation

Risk Summary

There is no information regarding the possibility of administered calcipotriene and betamethasone dipropionate in human milk, the effects on the breastfed infant, or the effects on milk production. Concentrations of calcipotriene in plasma are low after topical administration, and therefore, concentrations in human milk are likely to be low. It is not known whether topical administration of large amounts of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Enstilar® Foam and any potential adverse effects on the breastfed child from Enstilar Foam or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breast milk, use Enstilar Foam on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use

The safety and effectiveness of Enstilar Foam for the treatment of mild to severe plaque psoriasis have been established in pediatric patients age 12 to 17 years. The use of Enstilar Foam for this indication is supported by evidence from adequate and well-controlled trials in children and from one uncontrolled trial in 106 adolescents age 12 to 17 years with psoriasis of the body and scalp. Calcium metabolism was evaluated in all pediatric subjects and no cases of hypercalcemia or clinically relevant changes in urinary calcium were reported. Hypothalamic pituitary adrenal (HPA) axis suppression was evaluated in a subset of 33 pediatric subjects with moderate plaque psoriasis of the body and scalp (mean body surface area involvement of 16% and mean scalp area involvement of 56%). After 4 weeks of once daily treatment with a mean weekly dose of 47.4 mg/h, HPA axis suppression was observed in 3 of 33 subjects (9%). Because of a higher ratio of skin surface area to body mass, children under the age of 12 years are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. Pediatric patients are, therefore, at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids including Enstilar Foam.

Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients treated with topical corticosteroids. Local adverse reactions including striae have been reported with use of topical corticosteroids in pediatric patients. The safety and effectiveness of Enstilar Foam in pediatric patients less than 12 years of age have not been established.

Geriatric Use

Of the total number of subjects in the controlled clinical studies of Enstilar Foam, 97 subjects were 65 years and over, and 21 were 75 and over. No overall differences in safety or effectiveness of Enstilar Foam were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.3 mcg/kg/day in males (up to 56 mcg/m²/day and 39 mcg/m²/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When calcipotriene dipropionate was administered via oral gavage to male and female Sprague-Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (120, 360, and 1200 mcg/m²/day, respectively), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m²/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

PATIENT COUNSELING INFORMATION

Flammability

Instruct patients that Enstilar Foam is flammable; avoid heat, flame, or smoking when applying this medication.

Administration Instructions

• Shake before use and spray the foam by holding the can in any orientation except horizontally.
• Do not use more than 60 grams every 4 days.
• Discontinue therapy when control is achieved unless directed otherwise by the healthcare provider.
• Avoid use of Enstilar Foam on the face, underarms, groin or eyes. If this medicine gets on face or in mouth or eyes, wash area right away.
• Do not occlude the treatment area with a bandage or other covering unless directed by the healthcare provider. Instruct the patients not to use other products containing calcipotriene or a corticosteroid with Enstilar Foam without first talking to the healthcare provider.
• Wash hands after application.

Local Reactions and Skin Atrophy

Advise patients that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.

Hypercalcemia and Hypercalciuria

Advise patients that hypercalcemia and hypercalciuria have been observed with the use of Enstilar Foam.

HPA Axis Suppression, Cushing’s Syndrome, and Hyperglycemia

Advise patients that Enstilar Foam can cause HPA axis suppression, Cushing’s syndrome, and/or hyperglycemia.

Ophthalmic Adverse Reactions

Advise patients to avoid contact of Enstilar Foam with eyes and to report any visual symptoms.

Pregnancy and Lactation

• Advise pregnant women that Enstilar® Foam may increase the potential risk of having a low birth weight infant and to use Enstilar Foam on the smallest area of skin and for the shortest duration possible.
• Advise breastfeeding women not to apply Enstilar Foam directly to the nipple and areola to avoid direct infant exposure.

Manufactured by: LEO Laboratories Ltd., 285 Cashel Road, Dublin 12, Ireland or Colep Laupheim GmbH & Co. KG, Fockestraße 12, 88471 Laupheim, Germany (DE)

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JAK-STAT inhibition

an attractive target

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

Development of medications that inhibit the JAK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathway as treatment for a variety of inflammatory skin diseases is an active and promising area of research, says Jonathan H. Zippin, M.D., Ph.D., associate professor, departments of dermatology and pharmacology, Weill Cornell Medicine, New York, N.Y.

“Clinical trials are already underway evaluating oral JAK-STAT inhibitors that are licensed for the treatment of non-dermatologic diseases. Investigational topical formulations of these drugs are also being studied, as are a number of novel oral and topical JAK-STAT inhibitors,” Dr. Zippin says. “The experience with this class of drugs in dermatology is early, but preliminary results are encouraging, particularly for the locally applied agents that would minimize risk for systemic adverse events.”

JAK-STAT FUNDAMENTALS

Knowledge of the basic science of the JAK-STAT pathway along with the immune mechanisms and molecular signaling pathways involved in the pathogenesis of various inflammatory skin diseases provides a foundation for understanding interest in JAK-STAT inhibition as a therapeutic target.

The JAK-STAT pathway is an intracellular signaling pathway that is downstream of cytokines that are critical in the pathogenesis of various inflammatory skin diseases. It also regulates the production of inflammatory cytokines, Dr. Zippin says. He shared his insights with colleagues during the ODAC Dermatology Aesthetic & Surgical Conference in January.

The JAK-STAT signaling cascade is initiated upon cytokine binding to its respective extracellular receptor. The binding leads to JAK phosphorylation that is followed by translocation of STAT proteins into the cell nucleus. In the nucleus, the STAT proteins regulate the expression of genes that are responsible for the synthesis of cytokines and other mediators that act on various cell types, including immune cells (T cells, B cells, natural killer cells, critical T cells) and skin cells.

Both the JAK and STAT families are comprised of multiple members, and the various cytokines that are involved in the pathogenesis of different inflammatory skin diseases activate different combinations of JAKs and STATs. JAK-STAT inhibitors are small molecule drugs that prevent JAK activation.

“Drugs designed to inhibit the JAK-STAT pathway act at a level below the biologic agents that are currently used to treat inflammatory skin diseases. The biologics are monoclonal antibodies that block the activity of the pro-inflammatory cytokines either by binding to the cytokine or its extracellular receptor,” Dr. Zippin explains.

DERMATOLOGIC DISEASE TARGETS

Currently, the development of JAK-STAT inhibitors for use in dermatology is focusing on the treatment of atopic dermatitis, alopecia areata, vitiligo and psoriasis.

“We already have very good therapeutic options for atopic dermatitis and psoriasis, but JAK-STAT inhibition would offer another approach for the management of those diseases, and even offer a new topical treatment. On the other hand, there is great interest in developing JAK-STAT inhibitors for alopecia areata and vitiligo because of their unmet need for good therapies,” Dr. Zippin says.

Tofacitinib, which inhibits JAK1, 2 and 3, is being developed as a topical treatment for AD. Results of a randomized, double-blind, placebo-controlled phase 2a trial enrolling adults with mild-to-moderate AD showed that after four weeks, treatment with tofacitinib 2% was associated with an 82% reduction in mean EASI score compared with a 30% reduction with placebo. Additional trials with this topical formulation are now underway.

For alopecia areata, results have been published from studies evaluating oral tofacitinib (Xeljanz, Pfizer) and oral ruxolitinib (Jakafi, Incyte), which inhibits JAK1 and 2. Both of these agents are also being developed as topical products that are being investigated as treatment for alopecia areata in ongoing clinical trials.

In a study of oral tofacitinib as treatment for alopecia areata, almost two-thirds of the 66 enrolled patients experienced some hair regrowth and approximately one-third of patients achieved a >50% improvement in the disease severity score (SALT). Oral ruxolitinib showed promise in a case series involving 12 patients, of whom nine (75%) achieved an average of 92% hair regrowth after treatment for three to six months.

JAK-STAT CONTINUES ON PAGE 28
Differentiators in darker skin types

Eczema, or atopic dermatitis, is more common in patients with darker skin; yet, less is known about how to diagnose and treat patients with skin of color, according to Andrew Alexis, M.D., M.P.H., chair of dermatology at Mount Sinai St. Luke’s and Mount Sinai West, and professor of dermatology at the Icahn School of Medicine at Mount Sinai.

“Prevalence of childhood atopic dermatitis in white children is about 11%; whereas, for non-Hispanic black children, it’s 17%,” says Dr. Alexis, a speaker for the National Eczema Association.

Beyond the epidemiologic differences there are clinical and morphological differences in how eczema behaves in patients of color.

**CLINICAL DIFFERENTIATORS**

Eczema in darker skin types presents in unique ways, according to Dr. Alexis.

“The follicular presentation of eczema is more common in individuals with African ancestry. Another pattern called the lichenoid presentation of atopic dermatitis is more commonly seen in patients with African ancestry,” he says.

Eczema-related erythema, which presents as redness in lighter skin patients, is more challenging to perceive in the background of darkly pigmented skin. Instead of shades of red and pink, dermatologists might see lesions that appear violaceous, grayish, red-brown or very dark brown and can be confused with other conditions.

“Clinicians typically use erythema as one of the various markers of eczema. If there are challenges in detecting erythema itself there’s the risk of underestimating the severity of the disease. That has implications in the real-world clinical setting and the research setting, or clinical trial setting, where erythema is used as one of the measures for severity,” Dr. Alexis says.

One solution is for providers to calibrate their eyes to better detect erythema in patients with skin of color.

**“Prevalence of childhood atopic dermatitis in white children is about 11%, whereas for non-Hispanic black children it’s 17%.”**

Andrew Alexis, M.D., M.P.H.
Icahn School of Medicine at Mount Sinai.
New York

“What I mean by that is I like to look at the normal skin first, finding an area of uninvolved, non-lesional skin, so I can determine what the patient’s normal skin color is. Then I go to the areas of active, symptomatic eczema and basically assess the difference in color and texture in the lesional versus non-lesional skin,” Dr. Alexis says. “In doing that you get a much more accurate assessment of the erythema. It’s a better measure of severity.”

Another distinctive feature of atopic dermatitis in darker skin types is the tendency to develop pigmenary alterations of hyperpigmentation. This contributes to the burden of the disease. Not only do the patients endure the itching and the scaling and the other disturbances, but, once the lesions resolve, they tend to leave behind weeks to months of pigmentation change, which could also be disfiguring, according to Dr. Alexis.

**TREAT EARLY, AGGRESSIVELY**

One solution is to treat the atopic dermatitis early and aggressively.

“In light of the tendency to develop long-lasting pigmenary alterations, it makes it especially important to avoid under-treatment or delays in treatment and delays in diagnosis of atopic dermatitis. It’s particularly important to have effective long-term management of this chronic disease as opposed to intermittent management of flares,” Dr. Alexis says.

Managing only intermittent flares increases the burden of disease, in general, and contributes to greater post-inflammatory pigment changes in skin of color patients because of those repeated flares, he says.

One of the challenges of early treatment in skin of color patients is that dermatologists might be less likely to see these patients. Researchers reported in a study published in the *Journal of the American Academy of Dermatology* in 2017 that healthcare utilization among non-Hispanic black children with atopic dermatitis is lower than it is for white children with atopic dermatitis. But when non-Hispanic black children did see providers about their atopic dermatitis, their healthcare utilization became higher than for white patients.

This study suggests two things, according to Dr. Alexis. One, there may be disparities in the utilization and access to a healthcare provider for the treatment of atopic dermatitis. Two, the pattern of
Drugs designed to inhibit the JAK-STAT pathway act at a level below the biologic agents that are currently used to treat inflammatory skin diseases.

Jonathan H. Zippin, M.D., Ph.D., Weill Cornell Medicine, New York, N.Y.

JAK-STAT inhibition an attractive target FROM PAGE 26

Multiple case reports and case series have also been published describing benefit using either oral tofacitinib or ruxolitinib to treat vitiligo. Clinical trials with these oral medications are underway as is a pilot study investigating ruxolitinib 1.5% cream.

SAFETY
JAK-STAT signaling has pleiotropic effects and is involved in multiple homeostatic processes. Therefore, broad inhibition of JAK-STAT signaling has the potential for unwanted consequences that include increased risks of infection and malignancies, mild increases in serum lipids, and the development of certain cytopenias. These issues may be mitigated through the design of drugs that are highly selective for JAKs and STATs that are involved in disease pathogenesis and with topical versus oral administration.

“Oral JAK-STAT inhibitors have been used for several years with a reasonable safety profile so far, but it remains to be seen if problems will arise with longer term use. Therefore, as development of this class of drugs for dermatologic use continues, it will be important to identify compounds with a large therapeutic index,” Dr. Zippin says.

Disclosure:
Dr. Zippin is a consultant and advisor for Keith Therapeutics, has stock options (spouse) in Regeneron, and has received grant funding from Pfizer.

Differentiators of eczema in skin of color FROM PAGE 27

No one-size-fits-all approach.

“We see different types of eczema and different patterns in skin of color,” says Dr. Alexis. “It’s particularly important to be judicious with the use of topical corticosteroids, limiting the duration and making sure patients are educated about where to apply it and how long to apply,” Dr. Alexis says.

Dermatologists should also carefully consider the strength of the corticosteroids they’re prescribing in order to limit the development of steroid-induced hyperpigmentation, he says.

GAPS IN UNDERSTANDING
There remain gaps in understanding with respect to genetic differences among races and ethnicities with atopic dermatitis.

“For example, one genetic factor that is very common is atopic dermatitis patients of European ancestry is the filaggrin loss of function mutation. This is far less prevalent in patients of African ancestry with atopic dermatitis, which suggests there are other genetic factors that are more relevant to patients of African ancestry with atopic dermatitis,” Dr. Alexis says.

While more research is needed to examine the genetic and other factors that influence and contribute to atopic dermatitis in patients of all skin types, one thing that has emerged, according to Dr. Alexis, is that when it comes to diagnosing, treating and managing atopic dermatitis, there’s no one-size-fits-all approach.

Disclosure:
Dr. Alexis is a consultant and advisory board member for Ego,Celgene, Sanofi,AbbVie, and has received travel grants from Galderma and Regeneron.

Reference:
Laser therapy may be practical for some BCCs

ILYA PETROU, M.D. | Staff Correspondent

Laser therapy could be a practical management solution for patients with non-aggressive subtypes of basal cell carcinoma (BCC), according to authors of a recent review.1

Depending on the subtype of BCC, there are many different treatment modalities that a clinician can choose. Not all patients are amenable to all modalities due to compliance, tumor burden or contraindications. For nonaggressive BCCs, laser therapy could be a practical treatment and management solution.

Vascular-specific lasers have been increasingly studied for the treatment of BCC, specifically for non-aggressive BCCs including the superficial and nodular subtypes and may achieve good outcomes, according to authors Jusleen Ahluwalia, M.D., Mathew Avram, M.D., and Arisa Ortiz, M.D., department of dermatology, University of California, San Diego Health, La Jolla, Calif., and Massachusetts General Hospital, Boston.

“We foresee this therapy being as useful a modality as electrodesiccation and curettage is now to best address the basal cells selectively and through its mechanism of targeting the vasculature of the basal cells, but with minimal to no scarring,” Dr. Ahluwalia says. She is a second-year resident at the University of California, San Diego.

Laser therapy can also be of significant advantage in patients with Gorlin syndrome. These patients have to undergo repeated surgical or ED&C procedures for BCC removal, Dr. Ahluwalia says. They may also have compliance issues to prescribed topical therapies, leading to suboptimal treatment outcomes.

For nonaggressive BCCs including the superficial and nodular subtypes, laser therapy is proving very useful. However, for more aggressive subtypes such as the morpheaform BCC subtype, Dr. Ahluwalia says Mohs surgery is the highest standard of care and would be the treatment of choice because margins can be evaluated. The depth of the laser penetration injury of the lasers studied vary, ranging from a 1.5-mm depth with the pulsed dye laser (PDL) to 2.15 mm with the long-pulsed Nd:YAG laser.

“Pulsed dye lasers were initially employed because of their vascular specific wavelength leading to good treatment outcomes; however ... they do not achieve enough depth of injury. Although we use both devices, the long-pulsed Nd:YAG laser is often preferred,” she says.

For those BCC patients who defer from taking systemic vismodegib (Erivedge, Genentech) due to the potential for severe side effects, lasers could serve as a tool for drug-assisted delivery, hopefully reducing the potential of those side effects while maintaining drug efficacy.

“There is a relative lack of non-surgical treatment alternatives for BCC and the need for novel treatment approaches with less scarring is definitely there. While the current treatments for BCC are effective, they may be limited by patient preference or comorbidities, and in many cases, laser therapy can be a good treatment solution,” Dr. Ahluwalia says. ◄

Disclosures:
Dr. Ahluwalia reports no relevant disclosures.

Reference:
Maintenance therapy for BCC proves effective

ILYA PETROU, M.D. | Staff Correspondent

Administering a maintenance dose of vismodegib (Erivedge, Genentech) to patients with complete remission is important to stave off tumor recurrences, according to a recent study.1

The hedgehog inhibitor has long proven its efficacy in the treatment of locally advanced and metastatic basal cell carcinoma (BCC), however there is no clear guidance as to maintenance therapy when patients achieve complete remission.

Vismodegib selectively connects to the smoothened protein, deactivating the hedgehog pathway involved in the tumorigenesis process; thus, resulting in tumor growth inhibition. Before the dawn of the hedgehog inhibitors, treatment options for this patient population included surgery, chemotherapy or high-dose radiation therapy.

“Locally advanced BCC has always represented an uncommon, difficult-to-treat form of skin cancer, but approval of the hedgehog inhibitor vismodegib in 2012 has provided an effective treatment for patients affected by laBCC and those with metastatic BCC who are ineligible for surgery and/or radiotherapy,” wrote Alessia Villani, M.D., dermatology unit, department of clinical medicine and surgery, Federico II University of Naples, Italy, and fellow authors. Their study recently appeared in Dermatologic Therapy.

In the single-center study, researchers investigated the long-term efficacy of low-dose vismodegib in laBCC patients who achieved complete remission of their disease during a one-year follow-up period. The study included 42 patients (35 males, seven females; median age 75 years) who reported complete remission of their advanced BCC after vismodegib treatment of 150 mg/day, following histological confirmation of the complete regression of the BCC, and were subsequently divided into two groups. The first group of patients (n=27; 64%) continued with the “drug holiday” regimen consisting of a once-weekly maintenance dose of 150 mg vismodegib for one year after complete remission of their BCC, while the second group of patients (n=15; 36%) opted to discontinue vismodegib treatment and not take the maintenance dose following complete remission of their BCC due to more severe adverse events including alopecia and muscle pain.

Patients who continued a once-weekly maintenance therapy did not present with recurrence during a one-year follow-up period.

“Locally advanced BCC has always represented an uncommon, difficult-to-treat form of skin cancer, but approval of the Hedgehog inhibitor vismodegib in 2012 has provided an effective treatment for patients affected by laBCC and those with metastatic BCC who are ineligible for surgery and/or radiotherapy.”

Alessia Villani, M.D.  Federico II University of Naples, Naples, Italy, and colleagues

Results showed that those patients who continued with the once-weekly low-dose vismodegib maintenance treatment did not present with any new recurrence of BCC lesions during the one-year follow-up period, and only dysgeusia and muscle pain were reported as adverse events in 48% (13 of 27) and 29.6% (8 of 27) of patients, respectively. Although all of the previously reported adverse events had disappeared, those patients who decided not to continue with the vismodegib maintenance therapy reported a BCC recurrence rate of 26.6% (4 of 15 patients) during the same follow-up period.

The associated adverse events with hedgehog inhibitors can sometimes be challenging to tolerate, the most common of which include muscle spasms, hair loss, dysgeusia, nausea, vomiting, diarrhea, constipation and fatigue. These adverse events can lead to patient compliance issues and result in suboptimal clinical outcomes.

“There is no clear consensus as to maintenance therapy for patients affected by laBCC. The concept of a ‘drug holiday’ is not new. According to the study authors, many different dose reduction approaches during treatment have been proposed in order to increase a patient’s compliance and treatment adherence.

According to the study authors, the novel regimen of prolonged use of 150-mg low-dose vismodegib administered weekly over one year after complete remission of advanced BCC proves to be an effective strategy in eliminating skin tumor recurrence and in reducing the severity of the common adverse events associated with the drug therapy.

“Further randomized controlled studies involving a larger number of patients are required to better confirm the utility of a continuous treatment with vismodegib after the complete remission of BCCs and to define the best treatment strategy for each patient,” the authors write.

Disclosure: The authors report no relevant disclosures.

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*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.
Warnings and Precautions (cont’d)

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

- **Diarrhea, Nausea, and Vomiting**: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

- **Depression**: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

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

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

**Adverse Reactions**

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

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**NEW OTEZLA CLINICAL DATA FOR ADULTS WITH MODERATE TO SEVERE SCALP PSORIASIS**

**THE ONLY ORAL THERAPY WITH DATA IN THE LABEL FOR SCALP PSORIASIS**

- **A FIRST STEP TO SYSTEMIC THERAPY FOR MODERATE TO SEVERE SCALP PSORIASIS**

- **OTEZLA IS A NON-BIOLOGIC THERAPY WITH ORAL DOSING, A PROVEN EFFICACY AND SAFETY PROFILE, AND NO LABEL-REQUIRED LAB MONITORING**

**STYLE clinical trial**

**Study design**: Phase 3 multicenter, randomized, double-blind, placebo-controlled study of 303 patients with moderate to severe plaque psoriasis of the scalp. Patients were randomized 2:1 to Otezla® (apremilast) 30 mg twice daily (n=201) or placebo (n=102) for the placebo-controlled phase through week 16, then continued or switched to Otezla for the open-label extension phase through week 32. Treatment groups were stratified by baseline ScPGA score (3 [moderate] or 4 [severe]).

**Selected inclusion criteria**: Patients had moderate to severe plaque psoriasis of the scalp (ScPGA ≥3, SSA ≥20%), inadequate response or intolerance to ≥1 topical therapy for plaque psoriasis of the scalp, and moderate to severe plaque psoriasis (BSA involvement of ≥10%, sPGA ≥3, PASI score ≥12).

**BSA, body surface area; PASI, Psoriasis Area and Severity Index; ScPGA, Scalp Physician Global Assessment; sPGA, static Physician Global Assessment; SSA, scalp surface area.**

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*Data includes information derived from Symphony Health Solutions. The unprojected dataset covers 60%-70% of all commercially insured claims, Medicare, Medicaid, and cash prescriptions. Patients are classified as new to brand (NTB) if over the last 12-month period the patient had not been on their current “brand.” NTB includes patients who have had no prior treatment history as well as patients who switched to a brand for the first time from a different prior therapy [April 2014 through January 2020].*
For adult patients with moderate to severe plaque psoriasis

OTESLA SIGNIFICANTLY IMPROVES SCALP RESPONSE

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

Otezla patients

as likely to achieve scalp improvement
at week 16
vs placebo in the STYLE 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

Week 16
ScPGA: 0
3-point improvement in ScPGA score

Adverse reactions

- 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

Visit OtezlaPro.com for additional information

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://motherstobaby.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


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04/20 US-OTZ-20-0560

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

AMGEN
nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily

**OTZE® (apremilast) tablets, for oral use**

**Brief Summary of Prescribing Information**

 instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

ADVERSE REACTIONS

**Clinical Trials Experience**

between 0.5% and 10% of body weight occurred in 12-19% (768) of subjects treated with OTEZLA compared to 5% (19382) treated with placebo. Weight decrease of 20% of body weight occurred in 2% (1768) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3382) subjects treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss should be evaluated, and discontinuation of OTEZLA should be considered [see Adverse Reactions (6.1)].

**Drug Interactions**

Co-administration of strong cytochrome P450 enzyme inducers, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of rifampin 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. Pediatric Use

the safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

**Contraception**

that OTEZLA is contraindicated in patients with a known hyperresponsiveness 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 no reports of 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 the healthcare provider should be alert for the need to alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

**Pediatric Use**

Abbreviated exposure is decreased when OTEZLA is co-administered with strong CYP3A4 inducers (such as rifampin) and may result in loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)].

**Drug Interactions**

Co-administration of strong cytochrome P450 enzyme inducers, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of rifampin 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. 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 1425 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the efficacy and safety in elderly subjects 65 years of age and younger adult patients < 65 years of age in the clinical studies. Of the 1257 subjects who enrolled in two placebo-controlled psoriatic arthritis trials (PSR-1 and PSR-2), a total of 108 psoriasis subjects were 65 years of age and older including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects 65 years of age and younger adult subjects ≥65 years of age in the clinical trials.

**Renal Impairment**

Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft-Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

**Hepatic Impairment**

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

**OVERDOSAGE**

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should be provided. Laboratory investigations: Weight, blood pressure, liver function tests, complete blood count, renal function tests, electrocardiogram.

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.

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**Hereditary melanoma tumor syndromes**

“When we talk about familial melanoma today, we are moving away from a pure focus on patient susceptibility to develop multiple melanomas and towards awareness that cutaneous melanomas may be part of a mixed tumor syndrome,” Dr. Tsao says. Dr. Tsao spoke about melanoma tumor syndromes at the 2020 Dermatology Foundation Clinical Symposium.

“For some patients, the melanoma or another diagnostic melanocytic tumor may be a harbinger of risk for other internal malignancies. Early identification of these patients can be important so that they can be referred to other specialists as appropriate for additional cancer screenings,” he adds.

**FAMMM SYNDROME**

Overall, only about 1% of patients with melanoma are thought to have a hereditary melanoma tumor syndrome. To date, a number of loci have been linked to hereditary melanoma, but the two most pronounced involve mutations in CDKN2A and BAP1 (BRC1-associated Protein 1).

Overall, a mutation in CDKN2A is thought to occur in approximately 40% of hereditary melanomas. Associated with the familial atypical multiple mole-melanoma (FAMM) syndrome, the CDKN2A mutation leads to loss of function for producing the tumor suppressor protein p16.

Not all individuals with the mutation develop melanoma. Data on differences in risk based on geographic area of residence indicate that sun exposure, or other co-inherited factors, also plays a role.

“Among people with a CDKN2A mutation, the risk of melanoma is about 90% for those who live in Australia, about 70% for people living in the United States, but only 50% to 60% for people living in Northern England,” Dr. Tsao says.

Dermatologic follow-up for patients with a CDKN2A mutation involves two to four skin exams annually and stringent sun protection. The CDKN2A mutation also puts patients at risk for pancreatic cancer, and so these patients are also referred for consideration of routine pancreatic cancer screening by gastroenterologists.

**BAP1 TUMOR SYNDROME**

BAP1 tumor syndrome is far less common than FAMM, but it is associated with a longer list of organ system cancers than FAMM. Dr. Tsao says the mnemonic CRUMB can be used to remember the neoplasms that are part of the BAP1 syndrome: Cutaneous bapomas/melanoma, Renal cell cancer, Uveal melanoma, Meningioma and Mesothelioma, Breast/ovarian carcinoma and Basal cell carcinoma mesothelioma, breast cancer, Lung, kidney and other cancers also occur.

The underlying mutation also affects the function of a tumor suppressor gene. The BAPI associated skin lesions are small, amelanotic, semi-translucent papules, plaques, or nodules. Previously identified as nevoid melanomas, there are many terms for these lesions but they popularly are referred to as “BAPomas.”

Histologically, the BAPomas can have very atypical features that can simulate malignancy and are thus often re-excised with narrow margins; however, they do not appear to be highly aggressive.

**TERT and members of the shelterin complex, such as POT1**

Germline mutations predisposing to melanoma and other types of cancer have been reported in these genes but the number of patients is so rare that it is difficult to do proper genotype-phenotype correlation studies at this time.

**Rarer melanoma tumor syndromes**

Recently discovered melanoma susceptibility genes also include a rare polymorphism in MITF (p.E318K), which occurs more often in people of European descent.

Patients with the germline MITF(p.E318K) variant often have atypical moles. Aside from melanoma, the association between the E318K variant and other cancers is somewhat controversial.

Dermatologic follow-up for these patients is generally scheduled once or twice a year.

“These patients are checked regularly because they have melanoma and atypical moles and not just because they carry the MITF mutation. The frequency of follow-up depends on how many melanomas and atypical moles they have,” he notes.

Dr. Tsao says he will also refer these patients to a kidney specialist who may follow them for renal cancer with a CT scan.

Most recently, germline mutations predisposing to melanoma have been reported in genes involved in telomere regulation, including TERT and members of the shelterin complex, such as POT1. Other types of cancers have also been observed in families harboring these mutations, but the number of patients is so rare that it is difficult to do proper genotype-phenotype correlation studies. Because they are so rare and only recently described, clinical guidelines for follow-up care of individuals with these mutations have not yet been developed.

“With our current ability to sequence and read the genome, we will continue to uncover many more germline mutations conferring high risk for melanoma. Many of these will be ‘private mutations’ that occur in small families or even individuals, which is exciting for biology but less relevant for the general melanoma population. Therefore, it will be a challenge to determine their significance for patient follow-up,” Dr. Tsao says.

**Disclosure:** Dr. Tsao has no relevant financial interests to disclose.
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Today’s most effective biologics

LISETTE HILTON | Staff Correspondent

Four biologics stood out among 15 injectable and oral medications as having the highest short- and long-term response rates for the treatment of moderate-to-severe plaque psoriasis, according to a meta-analysis published recently in *JAMA Dermatology*.1

“As dermatologists and dermatology providers, it can be confusing trying to decide among the various therapies that we have for psoriasis, especially at this time when we have a lot of different options,” says study author April W. Armstrong, M.D., M.P.H., a dermatologist and professor of dermatology and associate dean for clinical research in dermatology at the Keck School of Medicine of USC, Los Angeles. “In this study we performed a meta-analysis, where we took all the FDA and European Medicines Agency approved biologics and oral therapies and compared them in terms of their efficacy. We could do that because many trials that evaluate these medications are designed very similarly.”

Dr. Armstrong and colleagues studied data from 60 clinical trials, measuring Psoriasis Area and Severity Index (PASI) 75, 90 and 100 response rates at 10 to 16 weeks and 44 to 60 weeks from baseline. They found risankizumab (Skyrizi, Abbvie), brodalumab (Ablynx, Valeant Pharmaceuticals), ixekizumab (Taltz, Eli Lilly), and guselkumab (Tremfya, Janssen CarePath) had the highest 10-to 16-week and 44-to-60-week short- and long-term response rates.

Results at weeks 44 to 60 were similar with risankizumab having PASI 90 rates of 79.4%, guselkumab at 76.5%, brodalumab at 74% and ixekizumab at 73.9%.

The researchers also studied secukinumab (Cosentyx, Novartis), infliximab (Remicade, Janssen CarePath), certolizumab pegol (400 mg) (Canvia, UCB), certolizumab pegol (200 mg), ustekinumab (Stelara, Janssen CarePath), adalimumab (Humira, Abbvie), tilikizumab (200 mg) (Ilumya, Sun Pharma), tilikizumab (100 mg), etanercept (Enbrel, Amgen), apremilast (Otezla, Amgen), dimethyl fumarate (Tecfidera, Biogen) and placebo.

For comparison, the estimated PASI 90 response rate at 10 to 16 weeks for apremilast was 12.1%, etanercept was 17.9%, adalimumab was 43.7%; ustekinumab was 43.9%, infliximab was 57.4% and secukinumab was 61.4%.

“Practitioners can reference this article because it talks about how these drugs compare in regard to efficacy, by a specific time and looking at specific outcomes. For example, if they want to know if biologic A is better than biologic B in terms of the proportion of patients that will get clear by week 60, they might look at this particular article and get a good sense of that,” she says.

Efficacy is only part of the picture. It’s also important to think about a medication’s ability to treat psoriatic arthritis and its safety record; however, safety is one thing the authors did not look at because many studies are not powered for safety comparisons, Dr. Armstrong says.

It’s also important to individualize therapy, according to Dr. Armstrong. If a patient has psoriatic arthritis, for example, account for that when selecting a medication, she says, because all of the IL-17 inhibitors are approved for psoriatic arthritis, whereas IL-23 inhibitors are not currently.

Another consideration when individualizing therapy is patient comorbidities. Patients with demyelinating disease can’t be on a [tumor necrosis factor] TNF inhibitor. Or if they have a personal history of Crohn’s disease, then an IL-17 inhibitor might not be appropriate, Dr. Armstrong says.

“I think this article will be informative with regards to answering the question: ‘If I want to give this patient the best efficacy, which drug would give the best chance of achieving that?’”

As for where that leaves other medications that did not quite rise to the top, Dr. Armstrong says that if patients are on those drugs and are doing well, there’s no reason to switch.

“Those drugs still have an important role for patients. The older drugs probably have longer record of safety, so that’s very important. A lot of the newer drugs have robust efficacy, but they are relatively newer, so their long-term safety is not as established as the older drugs,” she says.

In addition, older drugs may have better access for patients than newer ones, she says.

Authors of an accompanying editorial note that network meta-analyses, like the one in the paper by Armstrong et al, rely on head-to-head comparisons within trials and indirect comparisons across trials.

“The strength of network meta-analyses is the ability to standardized drug effect across many trials,” the editorial authors wrote. “Indeed, the raw rankings of efficacy as determined by the Armstrong et al [network meta-analysis] and other recently published [network meta-analyses] offer a valuable starting point from which to initiate discussions with patients and improve shared decision making related to choosing the most appropriate psoriasis treatment.”

References:

Disclosures:
Dr. Armstrong reported to JAMA that she received grants and personal fees from AbbVie, Eli Lilly, La Jolla Pharma, and Novartis Pharmaceuticals Corp; personal fees from Boehringer Ingleheim/Pharmaco, Bristol Myers Squibb, Celgene, Dermavant, Janssen Pharmaceuticals Inc, Merck, Modernizing Medicine, Ortho Dermatologics, Pfizer Inc, Regeneron Pharmaceuticals, Sanofi Genzyme, Science 37 Inc, Genentech, Otsuka America, and Abbott; and grants from Dermira, Janssen Ortho, Novartis, and Pfizer. Dr. Armstrong also disclosed that she received institutional research funding from AbbVie, which markets Taltz (ixekizumab-rphony); funded the research and participated in discussions related to answering the question: ‘If I want to give this patient the best efficacy, which drug would give the best chance of achieving that?’

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Quick TAKES

Ixekizumab demonstrated safety, tolerability and efficacy in patients aged 6 to under 18. At 12 weeks, the proportion of patients achieving the co-primary endpoints was superior to placebo with statistically significant difference (P<0.001).

IxEKIZUMAB approved for pediatric plaque psoriasis

By MORGAN PETRONELLI | Assistant Editor

E li Lilly recently announced the U.S. Food and Drug Administration (FDA) has approved ixekizumab 80mg/mL (Taltz) for the treatment of pediatric patients (ages 6 to under 18) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The approval announcement follows positive results of a phase 3, 12-week, double-blind, randomized, placebo-controlled clinical study investigating the efficacy, tolerability and safety in 171 pediatric patients.

The children were randomly assigned to receive a weight-based dose of ixekizumab (20 mg for <25 kg, 40 mg for 25-50 kg or 80 mg for >50 kg, with 40 mg, 80 mg or 160 mg starting doses, respectively) or placebo up to week 12.

Co-primary endpoints included the proportion of patients who achieved a static Physician’s Global Assessment (sPGA) of clear or almost clear skin (0,1) and at least a 75% increase from baseline on the Psoriasis Area and Severity Index score (PASI 75) at week 12. Secondary endpoints were a proportion of patients achieving sPGA (0), PASI 90, PASI 100 at week 12 and a minimum of four-point improvement in Itch Numeric Rating Scale (Itch NRS ≥4) among patients with baseline Itch NRS ≥4 at week 12, as well as PASI 75 and sPGA 0.1 at week four.

The proportion of patients who achieved the co-primary endpoints was superior (P<0.007) to placebo. Of patients treated with ixekizumab, 89% achieved PASI 75 vs. 26% who received placebo. Additionally, 81% of patients treated with ixekizumab achieved sPGA 0.1 vs. 11% of patients who received placebo.

"In the phase 3 pediatric study, half of patients treated with Taltz achieved completely clear skin after only 12 weeks of treatment. These results and the subsequent FDA approval make a strong case for Taltz as an effective treatment option for doctors to consider,” says Jennifer Cather, M.D., Modern Research Associates, Dallas.

The safety profile examined in the study was consistent with previous safety profiles of ixekizumab except for the more frequent occurrences of influenza (2%), conjunctivitis (3%) and urticaria (2%). Also, this 12-week clinical trial exhibited higher incidences of Crohn’s disease in the ixekizumab group (0.9%) compared to the placebo group (0%).

Ixekizumab is a monoclonal antibody that targets the IL-17A (IL-17A) cytokine while inhibiting its interaction with the IL-17 receptor. It was initially approved in March 2016 for the treatment of moderate-to-severe plaque psoriasis in adults who are also eligible for phototherapy or systemic therapy. Since then, the drug has also been approved for the treatment of psoriatic arthritis in adults (December 2017) and ankylosing spondylitis in adults (August 2018).

“We have over five years of data demonstrating that Taltz is a safe and effective treatment option for psoriasis in adults, and with this approval, we’re pleased to now be able to offer Taltz to more people living with this challenging condition,” says Piotr Jonsson, senior vice president and president of Lilly Bio-Medicines.

Reference:


Quick TAKES

New apremilast data demonstrates efficacy of 30-mg close. Treated patients showed significant improvement in symptoms over 16 and 32 weeks. Safety profile resembled that of previous studies.

APREMILAST 30 mg safe, effective

By MORGAN PETRONELLI | Assistant Editor

Apremilast (Otezla, Amgen) significantly improved psoriasis symptoms in adults with mild-to-moderate disease, according to recently reported phase 3 clinical trial data.

Apremilast was approved by the U.S. Food and Drug Administration for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy, adult patients with active psoriatic arthritis and for adult patients with oral ulcers associated with Behcet’s Disease.

While apremilast is less effective than other injectable biologics, says Mark Lebwohl, M.D., Waldman Professor and Chair, Department of Dermatology, Icahn School of Medicine of Mount Sinai, New York, its major advantage is that it does not require needles.

“It’s a pill and is so safe that it does not require any monitoring—no blood tests or x-rays. In fact, some patients with limited disease prefer apremilast to using topical therapies. It’s simply easier,” Dr. Lebwohl says.

In a double-blind, multicenter, placebo-controlled trial, the ADVANCE study randomized 595 patients with mild-to-moderate plaque psoriasis to receive 30 mg of apremilast or placebo twice daily for 16 weeks. All patients then received treatment through an open-label extension study through week 32.

The 30-mg, twice daily dose achieved a statistically significant improvement compared with placebo, meeting the primary endpoint of the static Physician’s Global Assessment (sPGA) response (defined as an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline) at week 16.

Secondary end points were also met with a minimum of 75% improvement from baseline in percent of affected body surface area (BSA) as well as a change in BSA total score from baseline, and a change in Psoriasis Area and Severity Index (PASI) score from baseline.

The safety profile resembled that of previous studies, according to the company. The most common treatment-related adverse events that occurred in ≥5% of the patients included nausea, headache, nasopharyngitis, upper respiratory tract infection and diarrhea.

“Many patients with mild-to-moderate plaque psoriasis who use topical therapies still have challenges managing their psoriasis,” says David M. Reese, M.D., executive vice president of research and development at Amgen. “We look forward to discussions with the FDA about the potential to bring Otezla, which has already been prescribed to hundreds of thousands of patients with moderate-to-severe psoriasis, to more patients who may need additional therapeutic options.”

References:

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“We should play a role in making sure that these patients deal with their comorbidities well.”

Mark Lebwohl, M.D., Icahn School of Medicine, Mount Sinai, New York City, NY

Comorbidities: Dermatologists key to coordinating multispecialty care

As the utility of screening tools such as the Psoriasis Epidemiology Screening Tool remains controversial outside populations for which they were developed, the guidelines leave choosing particular tools up to the practitioner.

“Simply asking if a patient has joint pain is a very easy screening tool,” Dr. Lebwohl adds.

EVALUATE EARLY FOR PSORIATIC ARTHRITIS

Every patient should be asked about joint pain, he says. Psoriatic arthritis (PsA) impacts around one-third of patients with psoriasis, with an average onset time of 10 to 11 years after a psoriasis diagnosis, although it can occur at any point, even before psoriasis of the skin starts.

“If patients have joint symptoms, then those need to be evaluated and treated because we are often seeing patients early in the course of psoriatic arthritis. And there’s no question that if you treat it early, patients have a better outcome.”

To avoid the significant morbidity that can include joint damage, guidelines stress the need for appropriate education of patients and dermatologists about the signs and symptoms of PsA and the consequences of delayed diagnosis and treatment. The fact that PsA correlates with greater risk for diabetes and cardiovascular disease underscores the importance of timely recognition and management.

As the utility of screening tools such as the Psoriasis Epidemiology Screening Tool remains controversial outside populations for which they were developed, the guidelines leave choosing particular tools up to the practitioner.

“Simply asking if a patient has joint pain is a very easy screening tool,” Dr. Lebwohl adds.

RECOMMEND CVF ASSESSMENT

Many psoriasis comorbidities lead to heart disease, and psoriasis itself is an independent risk factor for heart disease, Dr. Lebwohl says.

“While the exact mechanism of this association is unclear,” the guidelines state, “it likely involves humoral and cellular inflammatory mediators, which are also important in the generation of atheriosclerosis and other cardiovascular risk factors.”

The prevalence of hypertension, obesity, smoking and metabolic syndrome and its comorbidities, including diabetes, are all increased in psoriasis.

“We should play a role in making sure that these patients deal with their comorbidities well. We’re not going to treat their hypertension, hypercholesterolemia or hypertriglyceridemia. But we should make sure that those get taken care of by their internist or cardiologist,” Dr. Lebwohl says.

A typical 10- or 15-minute dermatology appointment does not permit going over every item on a patient’s medical history, he adds, but dermatologists should at least be aware of the powerful association between psoriasis and cardiovascular risk factors and disease.

Along with recommending cardiovascular risk assessment for all patients with psoriasis, guidelines suggest considering early and more frequent screening for hypertension, diabetes and hyperlipidemia in patients who are candidates for systemic therapy or have psoriasis involving more than 10% body surface area (Level B recommendations). Such patients’ risk scores should be multiplied by a factor of 1.5, and cardiovascular risk management including lifestyle modification should occur according to national guidelines.

The increased prevalence of psoriasis impacts dermatologists’ therapeutic choices, says Dr. Lebwohl.

“The increased prevalence of psoriasis impacts dermatologists’ therapeutic choices, says Dr. Lebwohl.

INFLAMMATORY BOWEL DISEASE

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“Some of the biologic treatments we use for psoriasis are also used for Crohn’s disease (ustekinumab, adalimumab [Humira, AbbVie], infliximab [Remicade, Janssen CarePath]) and certolizumab pegol [Cimzia, UCB]; some of the biologics we use have been associated with an increase in inflammatory bowel disease (IL-17 blockers).”

MENTAL HEALTH

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Regarding metabolic syndrome, all patients with psoriasis should have their blood pressure checked against national guidelines (Level A recommendation). Level B recommendations include informing all patients with psoriasis about their increased risk for metabolic syndrome, checking all patients’ lipid levels and determining the obesity status of patients with moderate-to-severe psoriasis. For patients with body mass index >40 kg/m² who fail standard weight-loss measures, consider bariatric surgery to improve comorbidities.

Mental Health

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1.1 In the absence of a 50% reduction in plaque size after 16 weeks of treatment, or if the patient’s condition is unchanged, or if the patient withdraws consent, the dose may be increased to 100 mg or 200 mg if the patient’s condition is unchanged, or if the patient withdraws consent, or if the patient’s condition is unchanged, or if the patient withdraws consent.

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Mark Lebwohl, M.D., Icahn School of Medicine, Mount Sinai, New York City, NY

Quick TAKES

Psoriasis carries a specific set of comorbidities that should be kept in mind when evaluating each patient.

Current joint psoriasis guidelines emphasize the need to help patients understand the relationship between psoriasis and comorbid conditions and the importance of seeking appropriate interventions.

“Simply asking if a patient has joint pain is a very easy screening tool,” Dr. Lebwohl adds.

DermatologyTimes.com  JUNE 2020

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Stem cell factor plays role in hyperpigmented skin

LISETTE HILTON | Staff Correspondent

Stem cell factor, a growth factor critical for melanocyte survival, plays an important role in the development of benign and malignant skin hyperpigmentation disorders. More research is needed to look at targeting stem cell factor inhibition as a way to treat skin lesions from melasma to melanoma, according to an article published December 2019 in the Asian-Pacific Journal of Cancer Prevention.1

Stem cell factor binds to the receptor tyrosine kinase and is expressed by the body’s fibroblasts and endothelial cells, promoting melanocyte differentiation proliferation, migration and survival, according to the authors.

“The interaction of stem cell factor with its receptor, c-kit, is well known to be crucial for the survival of melanocytes,” the researchers write. But little is known about the role of stem cell factor/c-kit interaction in epidermal pigmentation, according to the paper.

These researchers studied stem cell factor expression in benign and malignant pigmented lesions to determine the growth factor’s role in pathogenesis and potential use as a therapeutic target.

They studied stem cell factor expression in 60 patients with benign hyperpigmented lesions, including 20 with melasma, 20 with solar lentigines and 20 with freckles. They also studied 36 patients with hyperpigmented skin cancers, including 14 with basal cell carcinoma, 12 with squamous cell carcinoma and 10 who had malignant melanoma.

They found stem cell factor was positively expressed in all melanomas, solar lentigines and freckled lesions.

More specifically, immunohistochemical testing revealed significantly higher stem cell factor expression in melanoma lesions than in perilesional skin. They found moderate expression in 60% and strong expression in 40% of melanoma cases in melanoma lesions. While there was only weak expression in 100% of melanoma cases in perilesional areas.

The intensity of stem cell factor expression in lentigines lesions was weak in 10%, moderate in 30% and strong in 60% of cases, while perilesional areas in those cases had no stem cell factor expression in 20% of patients and weak expression in 80%.

Stem cell factor expression intensity was increased in the lesional parts of freckle cases, with weak expression in 20% of patients, moderate in 30% and strong expression in 50%. Stem cell factor was not expressed in 20% of perilesional areas in patients with freckles, weakly expressed in 70% and moderately expressed in 10% of perilesional areas.

Stem cell factor expression was significantly higher in basal cell carcinoma tumor cells compared with normal surrounding keratinocytes. The researchers found the squamous cell carcinoma cases they studied showed 50% cytoplasmic positivity for stem cell factor expression, suggesting stem cell factor is implicated in squamous cell carcinoma pathogenesis. Stem cell factor was also positively expressed in malignant melanoma.

While basal cell carcinoma, squamous cell carcinoma and malignant melanoma showed variable intensities of cytoplasmic expression of stem cell factor, the increase in expression in basal cell carcinoma and melanoma tumor cells was statistically significant, the authors write.

The researchers concluded their findings strongly suggest stem cell factor plays a key role in the development of common benign and malignant skin hyperpigmented disorders, but more research is needed to clarify that role. Studies looking at using stem cell factor as a target for developing new treatments for hyperpigmented disorders and malignancies also are needed. ▲

Disclosures:
The authors report no conflicts of interest, according to the paper.

Reference:
Perfecting the consultation

Excellent service does not equate to exceptional experience

ILYA PETROU, M.D. | Staff Correspondent

Perf ecting the cosmetic injectables consultation can be challenging. When offering in-office cosmetic procedures, the devil is in the details, according to one expert.

“It is paramount that the clinician establish trust with the patient to help overcome their concerns,” says Vince Bertucci, M.D., F.R.C.P.C., co-director, Dermatologic Laser Surgery and Aesthetic Dermatology Fellowship at the University of Toronto, Canada.

Building trust is a multifaceted process that starts with understanding that providing excellent service does not equate to creating an exceptional experience. According to Dr. Bertucci, the experience begins long before patients set foot in the practice. First impressions are very important. Every touch point must be carefully analyzed.

“Great staff answering the phones who can credential the office and succinctly answer queries, and a website that reflects clinic culture and the experience and services provided therein are but a few of the crucial first steps in establishing patient trust,” he says.

At the start of the consultation, Dr. Bertucci says it is important that physicians walk into the room calmly and politely introduce themselves using the patient’s name. Finding a common connection often helps to break the ice and build rapport. It is then the task of the physician to thoughtfully explain the consultation process so that the patient feels comfortable and at ease.

Physicians must carefully listen to the patient to understand their cosmetic concerns to glean information about the patient’s motivation and timing. Additionally, it is important to inquire about previous treatments and the patient’s level of satisfaction with these. A patient that has been to multiple physicians and is not satisfied with any of the results should be approached with caution as they may have unrealistic expectations.

After attentively listening to the patient and processing all this information, physicians then need to carefully observe the patient and see if their concerns and expectations are realistic.

“When contemplating a treatment plan for cosmetic patients, physicians should observe not just individual lines, wrinkles and folds, but should also assess the face as a whole to understand how all the parts fit together; thus, allowing for a more comprehensive approach and, ultimately, more natural results. Systematically considering the upper, middle and lower thirds of the face, the vertical fifths of the face, as well as harmony, balance, and proportion are critical when contemplating treatment options,” Dr. Bertucci says.

“[Patients] are sometimes hesitant to undergo treatment because what they really want is to look like the best version of themselves. To help overcome this, it is paramount that the clinician establish trust with the patient.”

Vince Bertucci, M.D.
University of Toronto, Canada

He suggests that physicians consider all therapeutic injectable options to address the patient’s cosmetic concerns starting from the forehead down to the neck, carefully weighing the options for each individual anatomical area and the impact it will have on other parts of the face.

According to Dr. Bertucci, a systematic approach with combination therapies is often the best route to help patients achieve their goals.

“After carefully assessing the face and considering the various options, treatments should be prioritized according to clinical impact allowing one to deliver the most meaningful results for any given budget. One of the benefits of performing a high impact treatment early on is that it helps enhance the patient’s confidence in the physician and permits the patient to better plan and prioritize future cosmetic treatments that align with their cosmetic goals,” Dr. Bertucci says.

Importantly, physicians also need to be able to distinguish between what the patient wants and what they actually need to achieve their cosmetic goals.

According to Dr. Bertucci, it is very important to be able communicate this important distinction. This can often be achieved utilizing before and after photos of patients with similar concerns.

“For example, patients often come in saying they want their nasolabial folds treated. Although treating the nasolabial folds may provide improvement, in many cases, nasolabial folds originate from cheek volume loss or from sleeping face down. So, treating the cheeks often times addresses the nasolabial folds while avoiding a simian appearance,” Dr. Bertucci says.

Educating the patient and explaining the interplay between the different areas of the face and how a suggested treatment plan would lead to cosmetic improvement that aligns with their cosmetic needs is paramount.

According to Dr. Bertucci, keeping the patient in the loop during every step of the process is requisite to building trust and avoids unwanted surprises from the first introduction to the last follow-up visit.

“The perfect cosmetic consultation is a continual work in progress and physicians have to adapt to the evolving challenges that patients bring. Feedback from patients is vital so that appropriate adjustments and fine tuning can be made and so that we can offer an even more exceptional experience,” Dr. Bertucci says.

Disclosures:
Dr. Bertucci reports no relevant disclosures.

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Chemical peels offer important advantages for treating melasma. Peeling is versatile, ranging from superficial to deep. Dermatologists can tailor peels to patients’ needs by choosing among several different types of exfoliating agents. Chemical peels are minimally invasive and relatively low cost. Italian researchers report in a paper published late last year in the *Giornale Italiano di Dermatologia e Venereologia*.

By applying one or more chemical ablative agents, dermatologists induce keratolysis or keratocoagulation on the skin’s surface. Priming the skin, usually with hydroquinone 2% to 4%, before peeling is crucial and should be done at least four weeks before any peeling treatment for melasma, regardless of the substance used. By choosing the right priming agent for patients’ needs by choosing among several different types of exfoliating agents. Chemical peels are minimally invasive and relatively low cost. Italian researchers report in a paper published late last year in the *Giornale Italiano di Dermatologia e Venereologia*. By applying one or more chemical ablative agents, dermatologists induce keratolysis or keratocoagulation on the skin’s surface. Priming the skin, usually with hydroquinone 2% to 4%, before peeling is crucial and should be done at least four weeks before any peeling treatment for melasma, regardless of the substance used.

Further peeling can inhibit DNA and RNA synthesis, as well as cell proliferation, including allergies, skin sensitization, dermatitis and itch. Clinicians treating melasma with kojic acid often use it in combination with exfoliating agents, such as mandelic or salicylic acid. Superficial peels with glycolic acid slightly exfoliate the skin, potentially without scabs, burns or redness, the authors write. Used in concentrations of 30% to 70% in melasma treatments, clinicians generally apply glycolic acid lotion or gel to the skin for one to five minutes. A few weeks after the initial treatment, melasma patients might need a series of four to six weekly treatments to get optimal results. Some clinicians combine glycolic acid with other compounds, such as hydroquinone, kojic acid, azelaic acid or salicylic acid. They might also combine peels with topical therapies, such as 10% glycolic based cream, to maintain results.

Salicylic acid is among the most widely used chemical peels. Dermatologists and others often use salicylic acid peels in strengths between 20% to 30% to eliminate epidermal pigment in the treatment of melasma. Salicylic acid peels are safe and generally well tolerated in patients of all skin types. Patients with tanned skin, active dermatitis, infection acute viral infection or pregnancy might not be candidates for salicylic peels, according to the paper.

The authors note the low-fluence 1064-nm Q-switched Nd:YAG laser used in conjunction with a modified Jessner’s peel has been shown to be preferred over treatment with the Q-switched Nd:YAG only, especially in dark skin patients with melasma. The combination offers better cosmetic results with fewer side effects and reduces the number of laser sessions needed, according to research cited in the paper.

**PROMISING MELASMA PEELS**

The authors cite studies that document promising options in chemical peeling for melasma, including:

- Cysteamine 5% cream, which showed significant efficacy in a randomized double-blind trial of 50 melasma patients.
- In a study of 50 melasma patients, researchers compared 4% hydroquinone to 5% methimazole once daily for eight weeks. Melasma improved in both groups but more so in the hydroquinone group. Nevertheless, researchers concluded that the noncytotoxic and nonmutagenic aspects of methimazole might make it an alternative in the treatment of melasma, whether used alone or in combination with other depigmenting drugs.

Researchers studying 1% flutamide cream versus 4% hydroquinone cream in 74 female melasma patients found topical flutamide appeared as effective, if not slightly more effective, than topical hydroquinone in treating melasma. But more studies are needed to confirm those results. And tranexamic acid, administered orally, topically or through microinjection or microneedling has been shown to reduce production of pro-melanogenic factors and decrease erythema and vascularization and is a promising melasma treatment, the authors write.

**References:**


**Quick TAKES**

- By applying one or more chemical ablative agents, dermatologists induce keratolysis or keratocoagulation on the skin’s surface.
- Skin appearance and texture improve after first treatment.
- While the gold standard remains hydroquinone, other commonly used agents include azelaic acid, glycolic acid, resorcinol, phytic acid, kojic acid, mandelic or salicylic acid, used alone or in various combinations.
PRACTICAL

“This is a very unique meeting; there’s nothing else like it. The personal touch you see at this meeting is very special. The different topics that were presented are amazing. It covers the whole spectrum of cosmetic surgery to running a practice. It’s a great meeting, and I can’t wait to come back next year.”

- DAVID GOLDBERG, MD

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- COREY MASS, MD

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Pipeline progress in epidermolysis bullosa

LISETTE HILTON | Staff Correspondent

Dermatologists and patients suffering from the rare genetic disorder epidermolysis bullosa (EB) have hope that their care will go beyond support wound dressings and bandages. For the first time, there are trials looking at therapies that actually heal EB wounds, according to Jean Y. Tang, M.D., Ph.D., professor of dermatology at Stanford University School of Medicine. These new therapies have not yet been approved, but there is access to many pipeline treatments through EB-dedicated clinics that are conducting research, like the one at Stanford, Dr. Tang says.

“Two years ago, there was nothing exciting on the horizon for potential therapies for EB,” she says. “Now we need EB patients to come and get tested for clinical trials because 2020 is going to be the year for EB.”

TARGETING THE COLLAGEN 7 GENE IN RDEB

Many of today’s pipeline therapies target the collagen 7 gene to treat one of the most severe EB types, recessive dystrophic EB (RDEB).

“One year we’re talking about targeted therapy—gene-specific therapy. In RDEB, patients are born with mutations in the collagen 7A gene, and they can’t make anchoring fibrils that connect the epidermis to the dermis. That’s why they’re called butterfly children because their skin is fragile as butterfly wings,” Dr. Tang says.

One such investigative therapy is EB-101 (Abeona Therapeutics), an autologous, gene-corrected cell therapy, lasts from six months to a few years, according to Dr. Tang. Researchers also are studying the systemic intravenously-delivered RDEB treatment PTR-01 (Phoenix Tissue Repair) in a phase 1/2 clinical trial.

“PTR-01 is an infusion of collagen 7 for patients with recessive dystrophic EB. I think this has great potential because it’s more or less replacing the protein that’s deficient in the condition. Because it’s given systemically, it really could help not just the skin but the internal manifestations of disease,” Dr. Tang says.

The hope is that we’ll have better treatments for patients. It’s very encouraging that there are so many pharmaceutical companies that are interested in helping patients with EB.”

Anna Bruckner, M.D.
University of Colorado Anschutz Medical Campus, Aurora, Colo.

EB-101 involves taking a biopsy of the patient’s skin, isolating fibroblasts and injecting corrected fibroblasts around the wound periphery.

“Several patients have already been treated and we have openings for more,” Dr. Tang says. The Fibrocell and Abeona trials include children with RDEB, she says. Fibrocell’s treatment is similar to that of Abeona’s EB-101, according to Dr. Bruckner.

“The difference is that the Abeona study is using the epidermis and making it into sheets. Whereas the Fibrocell study is injecting cells that normally live in the deeper layer of skin back into the skin. So, it’s a different cell type but the concept of creating cells that can make the protein correctly is similar,” Dr. Bruckner says.

And in June 2019, Krystal Biotech announced positive results from a phase 2 clinical trial for its pipeline gene therapy KB103, designed to deliver functional human collagen 7A1 genes to patients’ dividing and nondividing skin cells. The company claims its proprietary viral vector can penetrate skin cells more efficiently than other viral vectors. KB103 is a cream containing a virus with collagen 7, according to Dr. Tang.

THERE’S MORE…

AP101 (Oleogel-S10; Amryt Pharma) is available as a topical burn wound treatment in Europe, according to Dr. Bruckner.

“It is not really disease specific for EB. But I think the hope is that it might also help to improve wound healing and patient symptoms in EB,” Dr. Bruckner says. “Managing symptoms is really important. EB patients cite pain, itching and the burden of their wounds as things that are very bothersome. So, I do think that even if a treatment is not necessarily disease modifying but helps relieve the patient burden it has tremendous value.”

Researchers are conducting a phase 3 study for Oleogel-S10, which is now enrolling patients in the United States, according to the Dystrophic Epidermolysis Bullosa (Akebia Therapeutics)
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Research gains traction for hidradenitis suppurativa

WHITNEY J. PALMER | Staff Correspondent

For patients who have the inflammatory condition hidradenitis suppurativa, only one approved treatment has been available. However, efforts are underway to identify new therapeutic methods that can offer improved outcomes for these individuals, particularly those with more advanced disease.

According to Joslyn Kirby, M.D., a dermatologist with PennState Health Milton S. Hershey Medical Center, Hershey, Penn., the number of clinical trials investigating the efficacy of biologics in treating this condition at Stage 2 and Stage 3 are growing in number and should be considered a front-line treatment option. She discussed current and emerging hidradenitis suppurativa treatment options during the Fall Clinical Dermatology Conference in Las Vegas, October 17-20, 2019.

“We’re learning a vast amount about what’s happening in the skin with patients who have HS,” she says. “We’re looking at all the different cell types and cytokines that play an even greater role so we can modify these contributors to the pain, drainage and the incapacity of hidradenitis suppurativa. We’re hoping for even greater patient outcomes.”

Currently, she says, adalimumab (Humira, Abbvie) is the only medication approved by the Food & Drug Administration to treat hidradenitis suppurativa, and it targets TNF. But, the efforts to pinpoint biologics that can also be used to reduce symptoms are increasing. Between 2017 and 2019, the number of clinical trials devoted to this effort grew by 50%, she says, with many focusing on interleukin-17 and interleukin-23 inhibitors.

Although identifying the right clinical trial and enrolling patients might be difficult, Dr. Kirby says, better outcomes could develop if dermatologists suggest biologic therapy when they first see the scarring and tunneling associated with this condition. Providers and patients can find hidradenitis suppurativa clinical trials by going to bit.ly/HSclinicaltrials.

“The challenge occurs if a patient has inferior responsiveness to adalimumab,” she says. “They must go through a three-month wash-out period before participating in a clinical trial.”

The result, she adds, could be a delay in symptom relief.

TREATMENT OPTIONS

Currently, Dr. Kirby says, dermatologists can offer both medical and surgical treatments for the nodules and abscesses associated with Stage 1 hidradenitis suppurativa. Topical clindamycin, 15-percent topical resorcinol, oral doxycycline, spironolactone, adalimumab, and antibiotics can be used medically. With topical resorcinol, patients experience shorter flares, and lesions are 84-percent clinically resolved. Half of patients experience peeling, however.

Surgical options include 10mg-40mg interlesional steroid injections, punch de-roofing, laser hair removal, marsupialization, and excision. Between 25% and 33% of patients experience a lesion recurrence with punch de-roofing, she said.

Options are different for patients with Stage 2 and Stage 3 disease. Stage 2 patients experience nodules, abscesses, sinus tracts, fistula, and scarring, and Stage 3 patients can develop multiple sinuses, fistulas, and scars throughout an entire area.

For these individuals, if a clinical trial isn’t available, Kirby said, dermatologists can try the same medical and surgical therapies available to Stage-1 patients, but they can also add in infliximab and ustekinumab (Stelara, Janssen Biotech) as third-line medical options. She noted that interlesional steroid injections and punch de-roofing can be effective first-line options for Stage 2 disease, but recommended dermatologists pursue localized and regional excisions for Stage 3 patients who need surgical intervention.

TAKE-AWAY MESSAGES

Overall, Dr. Kirby says, it’s important for dermatologists to consider a combination of surgical and medical options when treating hidradenitis patients. And, whenever possible, she suggested providers begin pursuing a clinical trial as a potential first-line treatment method for patients who have Stage 2 or Stage 3 disease.

“Any tunnel formation — whether it’s one or multiples — indicates that a clinical trial is a great opportunity for people who haven’t received a biologic therapy before,” she said. “It’s a chance for them to get effective treatment, and an FDA-approved therapy is available later if it doesn’t work.”

“We’re learning a vast amount about what’s happening in the skin with patients who have HS.” Joslyn Kirby, M.D., PennState Health Milton S. Hershey Medical Center, Hershey, Penn.
Why is it so difficult to pinpoint reasons for inflammation in patients who develop atopic dermatitis?

In this Dermatology Times® podcast, Peter Lio, MD, provides in-depth analyses of both the “immune dysfunction” hypothesis and the “barrier defect” hypothesis. He discusses the presence of cytokines IL4 and IL13, contributory factors to inflammation, transepidermal water loss, targeted alternatives to traditional immunosuppressive treatments, and more.

Listen Now: [www.dermatologytimes.com/atopicdermatitis](http://www.dermatologytimes.com/atopicdermatitis)
Nano-pulse stimulation is an exciting new technology that likely has only touched the surface of its potential therapeutic utility in dermatology.

E. Victor Ross, M.D., Scripps Clinic Carmel Valley, San Diego, Calif.

New technology based on nano-pulse stimulation appears effective for non-melanoma skin lesions.

The CellFX™ system (Pulse Biosciences) delivers ultrafast pulses of high amplitude electrical energy to non-thermally clear the targeted cells. The high amplitude energy pulses cause the creation of tiny pores which allow ions such as calcium to move within the cells of the target lesion. This shift triggers a cascade of significant changes and disruption of vital cellular organelle function, ultimately leading to regulated cell death (RCD), or apoptosis. Adjacent non-cellular tissues remain unaffected and the non-viable cells are gradually removed via the natural healing process. This foundation has been proven in the early basic science studies.

"The system uses a very high amplitude electrical field and very short pulses. It’s not radiofrequency, but direct current, so it doesn’t have a specific frequency in the sense of most other electro-magnetic applications that are used in dermatology involving radiofrequency whether for aesthetic or non-aesthetic indications," Dr. Ross said.

Researchers at Pulse Biosciences recently focused their efforts on evaluating the device’s efficacy in treating a number of benign dermatologic lesions including sebaceous hyperplasia, seborrheic keratosis, verrucae, and acne, and have achieved excellent treatment outcomes. Interestingly, Dr. Ross says the NPS energy appears to be selective for cell rich lesions such as verrucae, seborrheic keratoses, sebaceous hyperplasia, and acne, compared to cell poor lesions.

"The mechanism of action is not a thermal one. Typically, in dermatology with the exception of photochemistry and photodynamic therapy, most of our applications involve heat, meaning there is either the transfer of electrical energy to heat or optical pulses in the sense of laser devices into heat. This new approach is unique in that now we are applying electrical pulse direct current, not radiofrequency," Dr. Ross says. "Even though the mechanism is not thermal, there is some pain involved during the procedure requiring local injectable anesthesia," he adds.

Aside from not requiring sometimes cumbersome eye protection, a central working advantage associated with the system is that it is noninvasive in the sense that there is no plume during treatment. One of the key issues when treating warts with different lasers is that there is a plume that activates HPV virus and needs to be suctioned during treatment. Of note, Dr. Ross says that the CellFX treatment in warts is thought to have a broader immune-stimulatory effect where the immune system appears to be stimulated around the targeted lesion as has been witnessed in the disappearance of untreated warts in the vicinity of the target lesion.

On this premise, researchers have now also begun a trial in nonmelanoma skin cancer to examine the potential therapeutic benefit of this effect in basal cell carcinoma. The hope is that there may be a peripheral stimulatory effect that would remove some of the tumor that is not removed directly by the device itself. According to Dr. Ross, these dermatologic indications may only be the tip of the iceberg concerning the broad utility of this treatment approach in dermatology.

"This is a unique technology for dermatology, or even beyond dermatology. The initial results of the trials have been excellent, and the applications for this technology will only grow. The excitement is also that I think we are moving faster than I would have thought two to three years ago, and for cell rich lesions, this seems to be an interesting technology that may have even more uses down the line in dermatology," Dr. Ross says. ◼

Disclosures: Dr. Ross reports no relevant disclosures.

Disclosure: Dr. Ross reports no relevant disclosures.

Watch the video on Nano-Pulse Stimulation in Dermatology.

EB pipeline progress}

Epidermolysis Bullosa Research Association of America (debra).

BIG STRIDES BUT WE’RE NOT THERE YET

EB care has improved dramatically in recent decades, as dermatologists and others have gained a better understanding of complications that these patients are likely to experience and ways that to address those early on, according to Dr. Bruckner.

"The hope is that we’ll have better treatments for patients. It’s very encouraging that there are so many pharmaceutical companies that are interested in helping patients with EB. This, I think, has been part of a sea change having to do with the FDA changing how it looks at rare diseases. The traditional approach to clinical trials really doesn’t work for conditions that don’t have a lot of affected people," Dr. Bruckner says. "Still, developing new therapies does take time, and we’re in the early part of that process. But I think it’s encouraging to see the momentum."

In the meantime, dermatologists should consider learning more about what’s in clinical trials by looking at ClinicalTrials.gov or debra.org. The CellFX™ system (Pulse Biosciences) is undergoing a trial in nonmelanoma skin cancer to examine the potential therapeutic benefit of this effect in basal cell carcinoma. The hope is that there may be a peripheral stimulatory effect that would remove some of the tumor that is not removed directly by the device itself. According to Dr. Ross, these dermatologic indications may only be the tip of the iceberg concerning the broad utility of this treatment approach in dermatology.

EB pipeline progress

EB Stewardship and Support

EB researchers have also been focusing on improving the care of patients with EB. Dr. Bruckner says that the EB community has made significant progress in recent years, with more awareness and resources dedicated to EB care.

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In the meantime, dermatologists should consider learning more about what’s in clinical trials by looking at ClinicalTrials.gov or debra.org and possibly referring patients to those, Dr. Bruckner says.

Dermatologists should also consider sending EB patients to EB centers, which usually are at academic centers or children’s hospitals, to see if there are ways that care could be optimized, according to Dr. Bruckner. ◼

Disclosures: Dr. Bruckner serves on the board for Castle Creek, Fibrocell, and Phoenix Tissue Repair and is also involved in the EB community. Dr. Ross serves on the board for Amryt and has consulted for Castle Creek in the past. Dr. Tang is an investigator with Phoenix Tissue Repair and Albeona.

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