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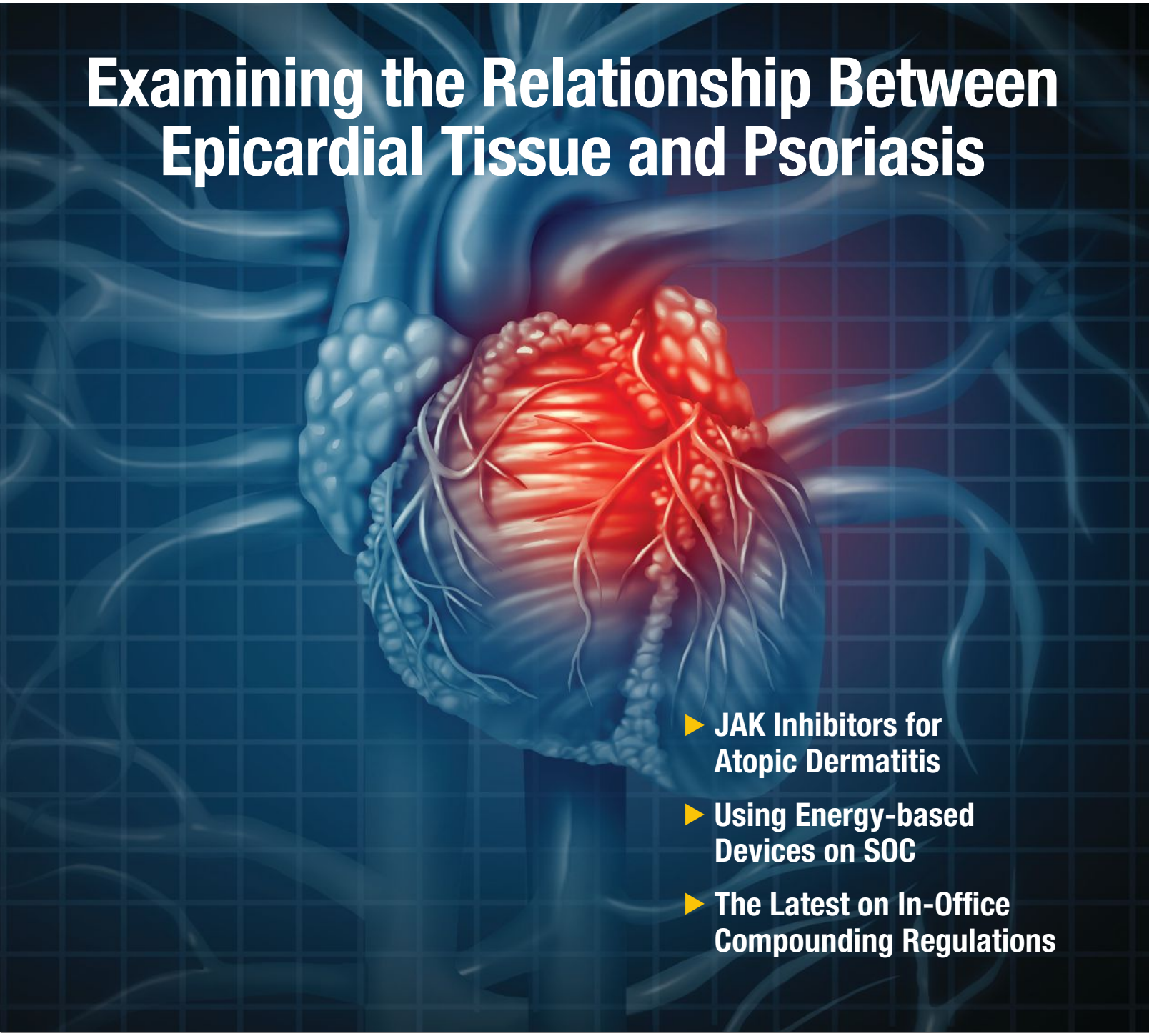
THE Dermatology Digest®

Vol. 3, No. 6 | June 2022

Examining the Relationship Between Epicardial Tissue and Psoriasis



- JAK Inhibitors for Atopic Dermatitis
- Using Energy-based Devices on SOC
- The Latest on In-Office Compounding Regulations

EDUCATIONAL • INTERACTIVE • AUTHORITATIVE

ITCH-SCRATCH-
ITCH-SCRATCH-
ITCH-SCRATCH-

THE ONE-OF-A-KIND
TOPICAL JAK INHIBITOR

For uncontrolled, mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥12 years[1]

- **Clear or almost clear skin** (IGA 0/1)* in >50% of patients at week 8 (53.8% vs 15.1% and 51.3% vs 7.6% vehicle†; $P<0.0001$)[1,2]
- **Meaningful itch relief** (Itch NRS4) in >50% of patients at week 8 (52.2% vs 15.4% and 50.7% vs 16.3% vehicle†; $P<0.0001$)[1,2‡]
  - **Itch NRS4 response seen as early as day 3** (18.4% OPZELURA vs 4.2% vehicle and 13.2% OPZELURA vs 0% vehicle†)[3]

OPZELURA was studied in 2 identically designed, double-blind, randomized, vehicle-controlled trials (TRue-AD1 and TRuE-AD2). The 2 studies included 1249 adult and adolescent patients ≥12 years of age with an affected BSA of 3%-20% and an IGA score of 2 or 3 on a severity scale of 0-4. Patients were randomized to monotherapy with OPZELURA, ruxolitinib cream 0.75%, or vehicle twice daily for 8 weeks.[1,2]

*With a ≥2-grade improvement from baseline.[1]

†In TRuE-AD1 and TRuE-AD2, respectively.[1,2]

‡≥4-point improvement in NRS among patients with a score of ≥4 at baseline.[1]

BID=twice daily; BSA=body surface area; IGA=Investigator's Global Assessment; JAK=Janus kinase; NRS=numeric rating scale.

Discover more at OpzeluraHCP.com

Incyte Dermatology

INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections.

If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on following pages.

Opzelura™
(ruxolitinib) cream 1.5%

IMPORTANT SAFETY INFORMATION for OPZELURA™ (ruxolitinib) cream 1.5% (continued)

SERIOUS INFECTIONS (continued)

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on following pages.

References: 1. Opzelura. Prescribing Information. Incyte Corporation; 2021. **2.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* Published online May 3, 2021. doi:10.1016/j.jaad.2021.04.085. **3.** Data on file. Incyte Corporation. 2021.

Opzelura™
(ruxolitinib) cream 1.5%

OPZELURA™ (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD); the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Thrombocytopenia, Anemia and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to 60 grams per week.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose *[see Use in Specific Populations]*.

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

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Contents

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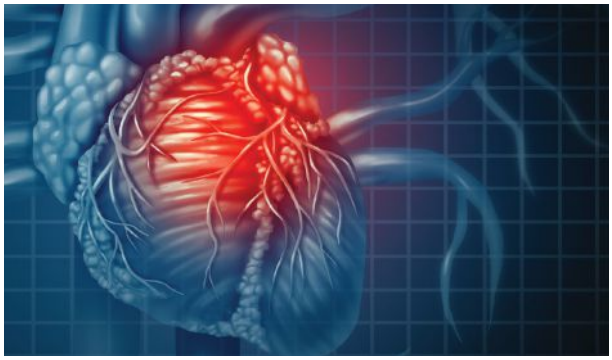
THE Dermatology Digest

***The Dermatology Digest* is Different**

Our multimedia approach delivers engaging and authoritative content in digestible bites for dermatologists overloaded with information in the emerging virtual environment. A distinct new concept, *The Dermatology Digest* filters practical and important information from industry meetings and develops original content for identified knowledge gaps in digital (video, podcast) and print formats. Concise, yet comprehensive, our content comes from the views, voices, and visions of leading dermatologists. As such, ours is an informative, educational approach thatemphasizes key details in support of safe, efficacious patient results.



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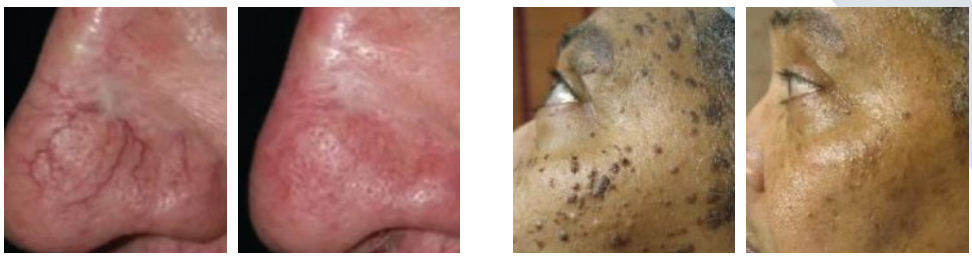

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IN THIS ISSUE

It is known that psoriasis patients are at increased risk for cardiovascular events. In this issue, Dr. Charles N. Ellis shares how measuring epicardial adipose tissue volume when psoriasis patients undergo computed tomography cardiac imaging could be an important opportunity for accurately assessing cardiovascular risk in these patients.

On the following pages, see our coverage of a range of topics important for dermatologists from the Atlantic Dermatology Conference, 41st ASLMS Annual Conference on Energy-Based Medicine & Science, 3rd Annual San Diego Dermatology Symposium, and 2022 American Academy of Dermatology (AAD) Annual Meeting. Meeting coverage is not only in print but also digital with video or audio on TheDermDigest.com.

In this issue, Dr. Camille Introcaso talks about the recently described reactive infectious mucocutaneous eruption (RIME) and what dermatologists need to know about diagnosing and treating it. Dr. Eliot Battle shares fundamentals for safely and effectively using energy-based devices to treat common concerns among skin of color patients. Dermatologist and candidate for the Missouri State Senate, Dr. George J. Hruza, updates readers on proposed changes to in-office compounding regulations and ongoing efforts to make dermatology's voice known. Dr. Sergei A. Grando offers a detailed approach to his multidrug protocol, which he has found can cure pemphigus and pemphigoid. Dr. Michael Ming presents current and future treatments aimed at prolonging survival in patients with early-stage malignant melanoma.

We continue with part 3 of our in-depth JAK inhibitor discussion, which up to now focused on the rheumatology experience. Part 3, the last of our series, is an engaging discussion between dermatologists Drs. George Martin and Ted Rosen about where JAK inhibitors fit in the systemic treatment armamentarium for atopic dermatitis.

In "Ted Talks," Editor-in-Chief Dr. Ted Rosen tackles the topic of betrayal in and out of dermatology. This month's Off-Label Pearl looks at using the JAK inhibitor upadacitinib for difficult-to-treat erosive lichen planus. And don't forget to test your diagnostic skills with the June Zebra that features the case of a 78-year-old male who developed a large, painless, thin-walled blister on his shin, which later ruptured but was followed by multiple smaller tense bullae near the first lesion.

We encourage your participation in *The Dermatology Digest* and invite you to contribute your own ideas for content! Have a Zebra that warrants sharing? Want to make content requests or share feedback? Contact us at Editorial@thedermdigest.com.

The Dermatology Digest

Ted Talks

What Does Betrayal Have to Do With Dermatology?

"Only trust thyself, and another shall not betray thee."

—William Penn (1644-1718)

Ted Rosen, MD, FAAD
Editor-in-Chief

This is Ted's take.
What's yours?
ted.rosen@thedermdigest.com

While there are many definitions of the word "betrayal," my favorite is: being harmed, physically or emotionally, by the intentional actions or omissions of a trusted person. In other words, unwanted and unexpected ills befall an individual due to the actions (or inactions) of someone who was trusted.

Among others, that "trusted person" could be a spouse, sibling, offspring, business partner, professional colleague, co-worker, neighbor, or friend.

Common forms of betrayal include disclosure of confidential information, sexual infidelity, theft, backstabbing, and disloyalty. Betrayal is ubiquitous; one might even say universal. As Albert Camus said, "I used to advertise my loyalty, but I don't believe there is a single person I loved that I didn't eventually betray."

The history of betrayal is long and colorful. Take, for example, the Old Testament stories of a brother's betrayal (Cain and Abel) and a lover's betrayal (Samson and Delilah). Of course, the most famous prototypical betrayal was Judas Iscariot's surrendering up Jesus Christ for 30 pieces of silver. Another infamous betrayal was Brutus taking part in the

The natural initial consequences of betrayal are surprise and confusion, followed shortly thereafter by shock, loss, and grief. These may be supplanted by anger and disgust.

assassination of his close friend and one-time political ally, Julius Caesar. A well-publicized modern betrayal consisted of a Ponzi scheme devised by financier and investment advisor, Bernie Madoff, whereby thousands of people—many of whom ostensibly his close friends—were collectively defrauded out of billions of dollars,

So, what does this have to do with dermatology? Believe or not, betrayal occurs within our realm as well. Let me give you just a few examples observed during my own career. How about the former resident who—after graduation—literally poached nursing staff from the very program which provided his dermatological training? Or the colleague with whom I worked closely on a project who surreptitiously submitted a poster for the AAD annual meeting—excluding my name! How about the dermatologist who submitted claims of immoral behavior to a professional ethics board simply to harass a competing rival in the same small market? Or the patient who left one practice only because of insurance coverage, who revealed that her new dermatologist was continually demeaning the prior one? How about the trusted receptionist who was selling patients' credit card numbers to members of the dark web? There are many more examples. Sooner or later you, too, will be betrayed.

The natural initial consequences of betrayal are surprise and confusion, followed shortly thereafter by shock, loss, and grief. These may be supplanted by anger and disgust. Severe, catastrophic betrayal can have long-term, devastating consequences, such as damaged self-esteem and self-doubt, admixed with measures of fear and shame.

The important question becomes: How best to deal with betrayal?

Although it might seem appropriate to seek revenge, retaliation is seldom productive.

Best to take some time to try and understand what happened and why. Was it simple carelessness? Was the betrayal motivated by greed or jealousy? Was it deliberately meant to be cruel?

At the same time, analyze the relationship. Was it really worth the time and energy you invested in it?

It might be helpful—even cathartic—to talk about this with a neutral third party. While it is advisable to initially avoid, as much as possible, the perpetrator of betrayal, eventually you need to confront the offender to tell them verbally or in writing how their actions made you feel then and how they still affect you.

Don't focus on the person responsible for the betrayal. Instead, focus on yourself. Start sentences with the word "I" and not with the word "You." That way, the betrayer won't be put immediately on the defensive.

Hopefully, the offender will understand, accept responsibility, and even apologize. Depending on how that conversation goes, you may choose to forgive the person. You may keep them in your life. On the other hand, it is typically best to cut ties with repeat offenders. ◈

RECOMMENDED READING:

Rachman S. Betrayal: a psychological analysis. *Behav Res Ther.* 2010;48(4):304-311. doi:10.1016/j.brat.2009.12.002.

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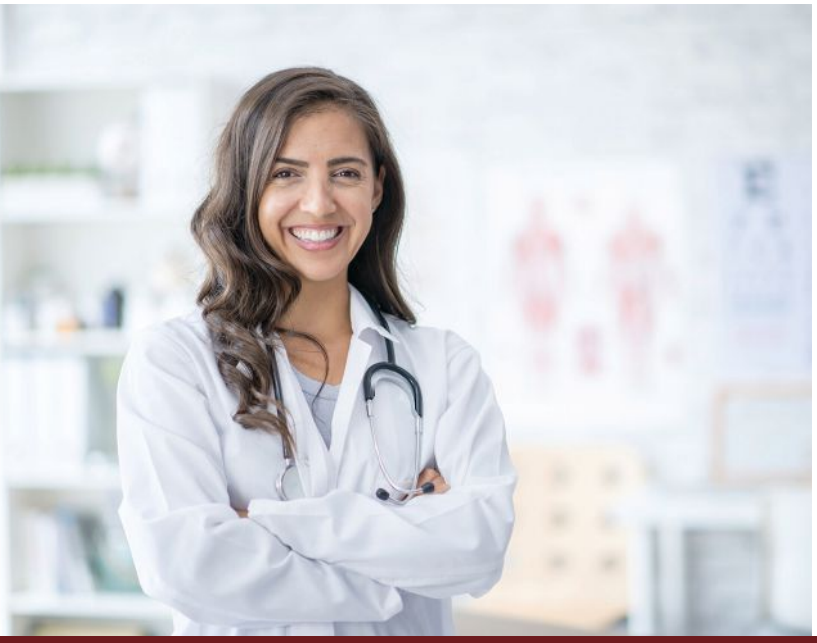

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Off-label Pearl

By Ted Rosen, MD, FAAD, Editor-in-Chief

JAK Inhibitor Upadacitinib for Erosive Lichen Planus

Erosive lichen planus, commonly encountered on the oral mucosa (Figure 1), is notably symptomatic (pain) and often difficult to treat.

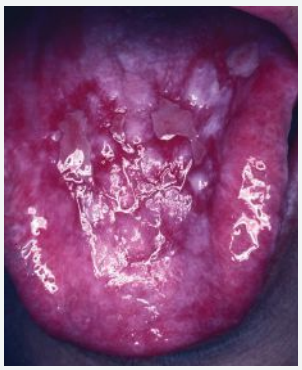
Topical ultrapotent and systemic corticosteroids are considered the first line treatments of choice. However, systemic steroids carry a plethora of potential side effects, and topical steroids may be difficult to utilize effectively in the mouth.

While topical calcineurin inhibitors (TCIs), especially pimecrolimus, are considered the second line therapy, the burning and stinging accompanying application may dissuade some patients from adherence to any regimen which includes TCIs.

Oral immunosuppressants are certainly convenient and frequently may be effective, but they include significant risks such as gastrointestinal intolerance, infection, and carcinogenesis. Mycophenolate mofetil is probably the safest of these drugs but is notoriously slow in its onset of action.

Therefore, we are still in search of a relatively safe, consistently effective, and convenient manner in which to treat oral erosive lichen planus.[1]

Recent work on the etiopathogenesis of lichen planus suggests substantial upregulation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.[2] Thus, it is not too surprising that a recent publication chronicled the nearly miraculous resolution of previously recalcitrant severe oral erosive lichen planus following the administration of the selective Janus kinase (JAK) 1 inhibitor, upadacitinib.[3]



The dose employed was 15 mg daily. This is also consonant with additional case reports of other lichen planus variants responding favorably to JAK inhibitors. I have now used this same modality—upadacitinib—to successfully treat both oral erosive and erosive esophageal lichen planus.

Of course, questions still remain. Which specific category of JAK inhibition will prove to be the most reliable therapy for erosive lichen planus? How durable will the positive effect be? Will any new, unexpected adverse events appear in conjunction with this type of treatment for this type of disease?

Still, I suggest that if you are faced with this really terrible disorder, where those afflicted sometimes can't even eat or speak comfortably, please remember and consider the JAK inhibitors.

REFERENCES

1. Gupta S, Ghosh S, Gupta S. Interventions for the management of oral lichen planus: a review of the conventional and novel therapies. *Oral Dis.* 2017;23(8):1029-1042. doi:10.1111/odi.12634.
2. Shao S, Tsoi LC, Sarkar MK, et al. IFN-γ enhances cell-mediated cytotoxicity against keratinocytes via JAK2/STAT1 in lichen planus. *Sci Transl Med.* 2019;11(511):eaav7561. doi:10.1126/scitranslmed.aav7561.
3. Balestri R, Bortolotti R, Rech G, et al. Treatment of Oral Erosive Lichen Planus With Upadacitinib. *JAMA Dermatol.* 2022;158(4):457-458. doi:10.1001/jamadermatol.2022.0147

Literature Lessons

GENERAL DERMATOLOGY

A small (N = 11) retrospective chart review revealed that a majority of patients with **SWEET SYNDROME** responded to oral dapsone therapy. The median daily dose was 100 mg (range 50 mg to 150 mg). Eight of 9 responders maintained disease control, without flares, for a median time of just under 1 year.

TO READ MORE: Hrin ML, et al. Dapsone as corticosteroid-sparing therapy for Sweet syndrome. *J Am Acad Dermatol*. 2022;86(3):677-679. doi:10.1016/j.jaad.2021.02.067.

A case of the rare **ICHTHYOSIFORM VARIANT OF SARCOIDOSIS** was presented. An accompanying literature review disclosed that this form of cutaneous sarcoid is most common in middle-aged Black women and favors the lower and upper extremities. In addition to dermal sarcoidal granulomas, other histological features resemble those found in ichthyosis vulgaris. Of note, over 90% of those with ichthyosiform sarcoid had extra cutaneous organ involvement.

TO READ MORE: Chen HW, et al. Ichthyosiform sarcoidosis: Report of a case and comprehensive review of the literature. *Int J Dermatol*. 2022;61(4):390-400. doi:10.1111/ijd.15604.

A retrospective case-control study involving 337 **VITILIGO** patients were given a validated survey to evaluate them for post-traumatic stress. Some 30% of vitiligo patients demonstrated this aberration. Symptoms included: sleep disturbance, intrusive thoughts, situational avoidance, and irritability.

TO READ MORE: Liu JW, et al. Post-Traumatic Stress in Vitiligo Patients: A Neglected but Real-Existing Psychological Impairment. *Clin Cosmet Investig Dermatol*. 2022;15:373-382. Published 2022 Mar 5. doi:10.2147/CCID.S350000.

On April 19, the U.S. Food and Drug Administration (FDA) issued warning letters to 12 companies selling over-the-counter (OTC) skin lightening products containing **HYDROQUINONE** as the active ingredient. The FDA does not consider hydroquinone "generally recognized as safe and effective" (abbreviated as GRASE). This stems from regulations included in the CARES Act (Coronavirus Aid, Relief and Economic Security Act), which included not only COVID-19 response efforts, but also updated the method in which certain OTC drugs are regulated.

TO READ MORE: FDA works to protect consumers from potentially harmful OTC skin lightening products. U.S. Food and Drug Administration. April 19, 2022. FDA.gov. Accessed May 17, 2022.

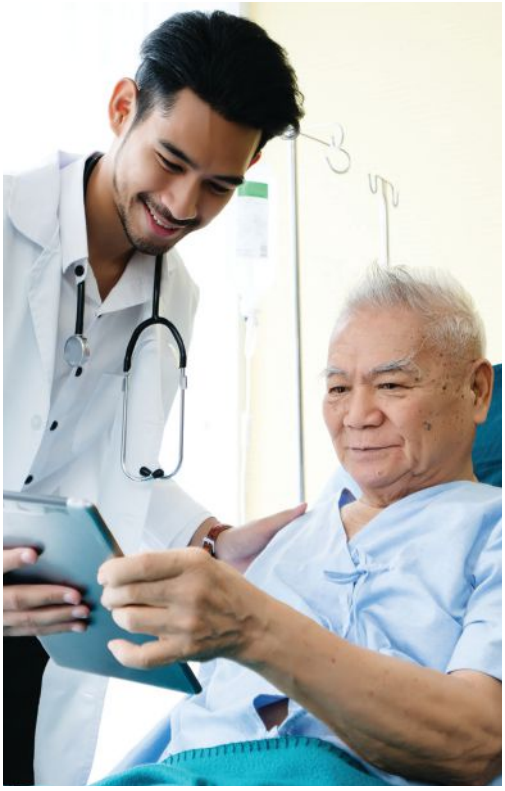
(**Editor's note:** OTC hydroquinone has essentially been banned in the United States, and these warning letters indicate that the FDA is taking this seriously.)

Investigators have perhaps discovered a manner by which to diagnose the severe neurodegenerative disease **AMYOTROPHIC LATERAL SCLEROSIS (ALS)** at an early stage. Researchers identified TDP-43 protein in the cytoplasm of dermal fibroblasts of individuals with ALS. The same protein was not found in dermal fibroblasts from either healthy controls or from a cohort of patients with Parkinson's disease and multiple sclerosis.

TO READ MORE: Rubio MA, et al. TDP-43 Cytoplasmic Translocation in the Skin Fibroblasts of ALS Patients. *Cells*. 2022;11(2):209. Published 2022 Jan 8. doi:10.3390/cells11020209.

GENERAL DERMATOLOGY *continued*

According to the authors of this commentary, **INPATIENT DERMATOLOGY CONSULTATIONS** are not appropriate for patients admitted due to extra-cutaneous disease. Other reasons inpatient dermatology consultations are not appropriate are if a patient is about to be discharged in < 48 hours, for chronic non-life-threatening dermatoses, for hospice care patients, or hemodynamically unstable patients. Examples of inappropriate inpatient consultations include: "rule out skin cancer" or "establish care for psoriasis."



TO READ MORE: Dobkin H, et al. When are inpatient and emergency dermatologic consultations appropriate? *Cutis* 2022;109;218-220. doi:10.12788/cutis.0492.

(**Editor's note:** Despite this logical algorithm, it is simply easier to obtain dermatological services while the patient is an inpatient (a "captive" audience), rather than rely on the inpatient to follow through after discharge.)

PSORIASIS

Imsidolimab, a humanized anti IL-36 receptor monoclonal antibody, is entering phase 3 studies for the acute and long-term management of generalized **PUSTULAR PSORIASIS**. Both efficacy and safety will be evaluated.

SOURCE: Gudjonsson JE, et al. Imsidolimab in the treatment of adult subjects with generalized pustular psoriasis: Design of a pivotal Phase 3 clinical trial and a long-term extension study. Presented at the American Academy of Dermatology Annual Meeting. Boston, Massachusetts. March 25-29, 2022. Poster 34617

A retrospective review of 16 melanoma patients (10 invasive and 6 in-situ) treated for psoriasis with **APREMILAST** for 36 months did not demonstrate any melanoma recurrence. Literature review similarly verifies safety of apremilast therapy in melanoma patients.

TO READ MORE: Gambardella A, et al. Is Apremilast a Safe Option in Patients with History of Melanoma? A Case Series and a Review of the Literature. *J Clin Aesthet Dermatol*. 2022;15(2):23-25.

The presence of circulating cardiac high-sensitivity troponin I (cTnI) and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) in patients with psoriasis and psoriatic arthritis correlated with carotid artery plaque formation and incident cardiovascular events (MI, stroke). These **CARDIAC BIOMARKERS** proved as good as, but not superior to, the Framingham Risk Score, which takes into account age, sex, smoking habits, systolic blood pressure, hypertension treatment, diabetes, total cholesterol and high-density lipoprotein cholesterol levels. The prognostic utility of this information remains to be determined.

TO READ MORE: Colaco K, et al. Association of Cardiac Biomarkers With Cardiovascular Outcomes in Patients With Psoriatic Arthritis and Psoriasis: A Longitudinal Cohort Study [published online ahead of print, 2022 Mar 8]. *Arthritis Rheumatol.* 2022;10.1002/art.42079. doi:10.1002/art.42079.

A Korean cross-sectional study involved 37,999 patients with **PALMOPLANTAR PUSTULOSIS (PPP)**, 332,279 psoriatics patients and 365,415 dyshidrosis patients. Compared to dyshidrosis, PPP had a stronger association with cardiometabolic disease, inflammatory arthritis, and autoimmune diseases (including vitiligo). When PPP was compared to psoriasis, the risks of ankylosing spondylitis and Graves disease were higher.

TO READ MORE: Kim DH, et al. Risks of Comorbidities in Patients With Palmoplantar Pustulosis vs Patients With Psoriasis Vulgaris or Pompholyx in Korea [published online ahead of print, 2022 Apr 27]. *JAMA Dermatol.* 2022;e221081. doi:10.1001/jamadermatol.2022.1081.

PEDIATRIC DERMATOLOGY

In the pediatric population, **LICHEN PLANUS (LP)** can present in a wide variety of ways. Notably, linear LP is more common and oral lesions less common, when compared to adults. Topical and oral corticosteroids are the most effective therapeutic interventions.

TO READ MORE: Merhy R, et al. Pediatric lichen planus: a systematic review of 985 published cases. *Int J Dermatol.* 2022;61(4):416-421. doi:10.1111/ijd.15678.

TMB-001, topical formulation of isotretinoin in a specialized delivery system (Timber Pharmaceuticals), has been granted fast track designation by the FDA for the treatment of congenital x-linked recessive ichthyosis and autosomal recessive lamellar ichthyosis. Earlier studies involving this agent were positive.

TO READ MORE: Timber Pharmaceuticals Announces Fast Track Designation Granted by FDA for TMB-001 in SEVERE SUBTYPES OF CONGENITAL ICHTHYOSIS. Timber Pharmaceuticals press release. April 28, 2022. Accessed May 17, 2022.

ATOPIC DERMATITIS

Among prior **DUPILUMAB NONRESPONDERS**, EASI-75 was obtained in 80.0% and 67.7% in those who received abrocitinib 200 mg and 100 mg daily, respectively. The higher daily abrocitinib dose also resulted in 77.3% of recipients achieving a > 4-point improvement in Peak Pruritus Numerical Rating Scale, while this measure of itch improved in 37.8% of those who received the lower abrocitinib dose.

TO READ MORE: Shi VY, et al. Phase 3 Efficacy and Safety of Abrocitinib in Adults with Moderate-to-Severe Atopic Dermatitis After Switching from Dupilumab (JADE EXTEND) [published online ahead of print, 2022 Apr 16]. *J Am Acad Dermatol.* 2022;S0190-9622(22)00608-9. doi:10.1016/j.jaad.2022.04.009.

A retrospective study of a large electronic record database, including only patients 60 to 99 years old, disclosed a 27% increased **RISK OF DEMENTIA** among those with atopic dermatitis. Among those with atopic eczema, the incidence of dementia was 57/10,000 person-years (95% CI, 56-59), compared with 44/10,000 person-years (95% CI, 44-45) in those without eczema. Perhaps the chronic inflammation associated with atopic dermatitis predisposes to neurodegenerative disease.

TO READ MORE: Magyari A, et al. Adult atopic eczema and the risk of dementia: A population-based cohort study [published online ahead of print, 2022 Mar 30]. *J Am Acad Dermatol.* 2022;S0190-9622(22)00541-2. doi:10.1016/j.jaad.2022.03.049.

COSMETIC DERMATOLOGY

A known side effect of botulinum toxin injections in/near the glabella is **EYELID PTOSIS**. While this can be reversed by intraocular drops, this case report demonstrated the same effect using brimonidine 0.33% gel (Mirvaso). There is less risk of systemic absorption utilizing the topical gel to correct this transient cosmetic adverse event.

TO READ MORE: Alotaibi GF, et al. Eyelid ptosis following botulinum toxin injection treated with brimonidine 0.33% topical gel. *JAAD Case Rep.* 2022;22:96-98. Published 2022 Jan 31. doi:10.1016/j.jdcr.2022.01.019.

Beware! Q-switched 1064nm **LASER HAIR REMOVAL** on the upper or lower lip can cause paradoxical and unwanted darkening of previously placed lip and lip border tattoos.

TO READ MORE: Al-Jasser MI, et al. Lip Tattoo Darkening After Q-Switched Laser Hair Removal Followed by Significant Spontaneous Improvement. *J Clin Aesthet Dermatol*. 2022;15(4):10.

HAIR AND NAILS

CHEMOTHERAPY-INDUCED PARONYCHIA is most commonly associated with administration of both classes of epidermal growth factor receptor (EGFR) inhibitors (examples: cetuximab, panitumumab, eroltinib, gefitinib, afatinib, and osimertinib) and taxane agents (examples: paclitaxel, docetaxel). The great toenail is most commonly affected, and the disease process typically starts 1 to 2 months after initiation of chemotherapy. Topical therapies include dilute bleach soaks, corticosteroids, and calcineurin inhibitors. These may be combined with oral tetracycline derivatives for severe cases.

TO READ MORE: Gupta MK, et al. Review of chemotherapy-associated paronychia. *Int J Dermatol*. 2022;61(4):410-415. doi:10.1111/ijd.15740.

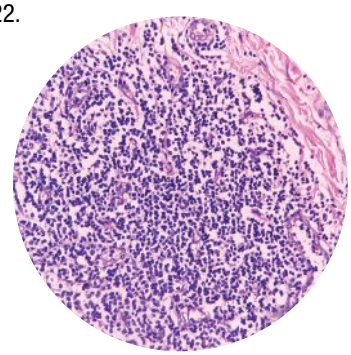
SCALP DYSESTHESIA (pain, burning, stinging without observable abnormality) may be due to stroke, brain tumor, vascular malformations, demyelinating disease, radicular compression, and underlying meningioma.

TO READ MORE: McConnell RD, et al. Scalp dysesthesia, more than skin deep. *JAAD Case Rep.* 2022;22:82-84. Published 2022 Jan 6. doi:10.1016/j.jdcr.2021.12.001

HIDRADENITIS SUPPURATIVA

A retrospective cohort study sourced from a large health record database compared 37,702 hidradenitis suppurativa patients to a similar number of matched controls. Compared to the control group, HS patients were at increased risk for rheumatoid arthritis, inflammatory bowel disease, myocardial and cerebral infarction, malignancy, and thromboembolic events. Notably, HS patients had increased C-reactive protein levels and higher erythrocyte sedimentation rates. CRP levels >10mg/L were predictive of a higher mortality rate.

SOURCE: Parthasarathy V, et al. C-reactive protein levels and circulating blood inflammatory markers are associated with poor outcomes in hidradenitis suppurativa patients: A multi-center cohort study. Presented at the American Academy of Dermatology Annual Meeting. Boston, Massachusetts. March 25-29, 2022.



A single-arm, prospective study, including 43 patients with Hurley stage I to III hidradenitis, evaluated success of **DEROOFING** as a means of disease management. Of the 123 lesions which were deroofed, only 7% had any recurrence 3 months post-operatively, and 93% reported no drainage at the surgical site.

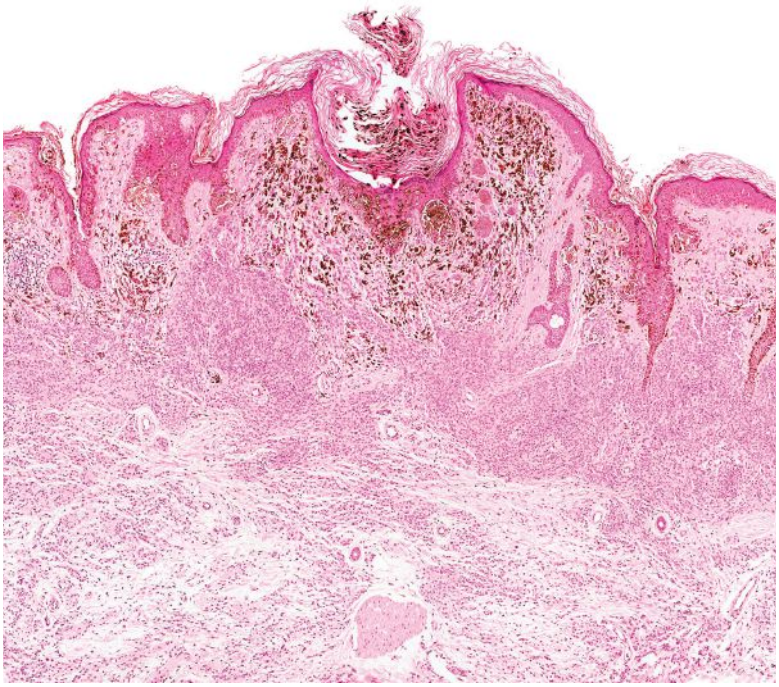
SOURCE: Vu TT, et al. Prospective study of surgical deroofing in the management of hidradenitis suppurativa. Poster. Presented at the American Academy of Dermatology Annual Meeting. March 25-29, 2022. Boston.

(**Editor's note:** Tracing out HS tracks with a probe, deroofing them, and then allowing healing by secondary intent is NOT a new concept. I did this when I was a resident in the 1970s!)

CUTANEOUS ONCOLOGY, SURGERY AND LASERS

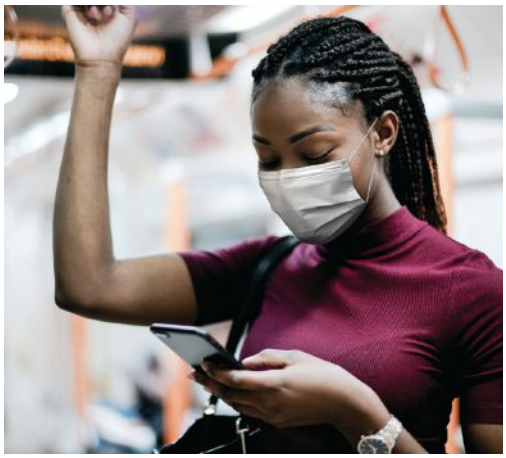
Nearly 444,500 solid organ transplant recipients identified from the Scientific Registry of Transplant Recipients were analyzed for incident **NONKERATINOCYTE SKIN CANCER**. From this cohort, 2380 transplant recipients were diagnosed with nonkeratinocyte skin cancer. Malignant melanoma constituted 61.8% of these lesions. Compared to the general population, the transplant recipients also had an increased risk of developing Kaposi sarcoma, Merkel cell carcinoma, and sebaceous carcinoma. Risk factors associated with nonkeratinocyte skin cancers in solid organ transplant patients included: older age at time of transplant, prolonged time since initial transplant, male gender, and excessive ultraviolet light exposure.

TO READ MORE: Sargen MR, et al. Spectrum of Nonkeratinocyte Skin Cancer Risk Among Solid Organ Transplant Recipients in the US. *JAMA Dermatol.* 2022;158(4):414-425. doi:10.1001/jamadermatol.2022.0036.



Based on the results of a large-scale observational study, investigators concluded that **SCREENING OLDER PATIENTS FOR MELANOMA**, especially men, may be cost-effective. Moreover, in this primary care based study, melanomas detected during specific screening sessions tended to be in situ or thin invasive (1 mm or less in thickness) compared to those detected in patients who had not attended one or more screening sessions.

TO READ MORE: Matsumoto M, et al. Five-Year Outcomes of a Melanoma Screening Initiative in a Large Health Care System [published online ahead of print, 2022 Apr 6]. *JAMA Dermatol.* 2022;e220253. doi:10.1001/jamadermatol.2022.0253.



ACNE

A group in India pointed out that **MASK-RELATED ACNE** is more common and more severe in skin of color. This relates to mask-induced increased skin temperature and humidity. The latter two factors lead to excessive sebum production (especially squalene) and swelling of keratinocytes with obstruction of pilosebaceous ducts.

TO READ MORE: Raju SP, et al. Mask Acne in Skin of Color: A Significant Dermatological Condition Amidst the COVID-19 Pandemic. *J Clin Aesthet Dermatol.* 2022;15(4):44-48.

ROSACEA

Rosacea patients who responded to subantimicrobial dose **DOXYCYCLINE** plus topical metronidazole 1% gel were randomly assigned to either receive placebo or continue on subantimicrobial dose doxycycline. After 40 weeks, those who remained on the modified-release doxycycline fared better, as their relapse rate was only 13.8% compared to 27.7% in the control group. Subantibiotic dose doxycycline seems to be a viable long-term management strategy for rosacea.

TO READ MORE: Del Rosso JQ, et al. Long-term inflammatory rosacea management with subantibiotic dose oral doxycycline 40 mg modified-release capsules once daily. *Dermatol Ther.* 2022;35(1):e15180. doi:10.1111/dth.15180.

One hundred forty-eight COVID patients without a **PRESSURE ULCER** who were admitted to the ICU for >24 hours were followed. Thirty-seven developed a pressure ulcer. Risk factors included higher body mass index (BMI), longer time spent in ICU, and evidence of consumptive coagulopathy. Notably, pressure ulcers were about 12 times more likely to develop in patients with a D-dimer level of >0.5ug/mL and a fibrinogen level of <2.0mg/mL on admission.

TO READ MORE: McLarney BD, et al. Predictors of COVID-19 disease severity augment the Braden scale in the prediction of pressure ulcer development among COVID-19-positive intensive care unit patients: A case-control study [published online ahead of print, 2022 Feb 25]. *J Am Acad Dermatol.* 2022;S0190-9622(22)00099-8. doi:10.1016/j.jaad.2022.01.021.

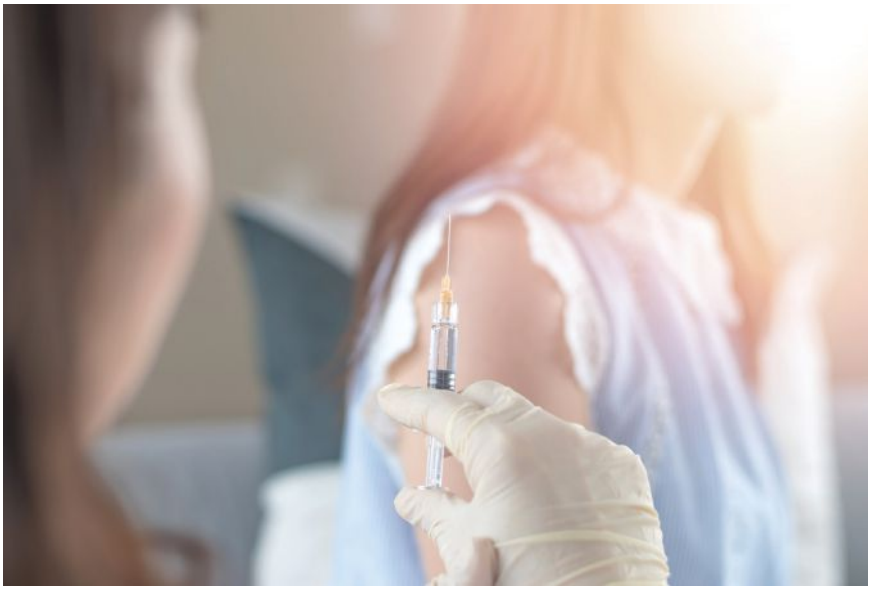
In a systematic literature review, investigators found that long COVID may be accompanied by **CUTANEOUS MANIFESTATIONS**. Not surprisingly, the most common was alopecia (probably telogen effluvium). However, of the 236 patients covered in this review, pernio-like lesions were seen in 4.2%, a maculo-papular eruption in 1.7%, persistent urticaria in 0.8%, and vesicular, papulosquamous, and purpuric lesions in 0.4% each. Lesions could arise as late as 6 months after initial COVID diagnosis and could last from as little as a week to as long as 240 days following COVID symptom resolution. Neither the mechanism nor the prognostic significance of such skin lesions is known.

SOURCE: Grover A, et al. Long-term cutaneous manifestations in COVID-19 patients: A systematic review. Presented at the American Academy of Dermatology Annual Meeting. Boston, Massachusetts. March 25-29, 2022.

The U.S. Food and Drug Administration issued an emergency use authorization (EUA) for a COVID-19 diagnostic test that detects chemical compounds in breath samples associated with SARS-CoV-2 infection. The test, **INSPECTIR BREATHALYZER**, can be performed in medical offices, hospitals, and mobile testing sites using an instrument about the size of a piece of carry-on luggage. In a large study of 2,409 individuals, the test was shown to have 91.2% sensitivity and 99.3% specificity.

TO READ MORE: Coronavirus (COVID-19) Update: FDA Authorizes First COVID-19 Diagnostic Test Using Breath Samples. FDA Press Release. April 14, 2022. Accessed May 17, 2022.

INFECTIOUS DISEASES



VACCINES TO PREVENT HPV-RELATED DISEASE (ano-genital tract squamous cell carcinoma and external genital warts) have been available since 2006. A comprehensive literature review disclosed that, among patients aged 9 to 26, those who received motivational or reminder text messages had higher initial vaccination rates and more timely subsequent vaccinations than comparable individuals who received no message.

TO READ MORE: Khuwaja SS, et al. Increasing HPV Vaccination Rates Using Text Reminders: An Integrative Review of the Literature [published online ahead of print, 2022 Mar 11]. *J Pediatr Health Care.* 2022;S0891-5245(22)00027-X. doi:10.1016/j.pedhc.2022.02.001

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Camille Introcaso, MD
Associate Professor of Medicine at Cooper Medical School of Rowan University, Camden, New Jersey

Understanding Reactive Infectious Mucocutaneous Eruption (RIME)

Dr. Camille Introcaso discusses reactive infectious mucocutaneous eruption (RIME), including the term's evolution, what RIME means to patients, and how to diagnose and treat it.

https://thedermdigest.com/video/understanding-reactive-infectious-mucocutaneous-eruption-rime

"RIME is an acronym for reactive infectious mucocutaneous eruption. This is a new term defined by Dr. Michele Ramien and colleagues in 2018 to distinguish patients who have erosive mucositis and cutaneous lesions caused by infection from patients whose condition is caused by drugs," said Camille Introcaso, MD, who presented "The Rhythms of RIME: Our Evolving Understanding of Reactive Infectious Mucocutaneous Eruption," at the Atlantic Dermatology Conference.[1,2]

RIME is characterized by four findings from a patient's history, physical exam, and evaluation, according to Dr. Introcaso.

"First, patients have an erosive mucositis of two or more mucous membranes. Second, skin lesions might be absent entirely or there may be sparse vesicular bullous or targetoid skin lesions. Third, patients have evidence of an infectious trigger. Fourth, the patient has not taken a medicine that could have caused the eruption."

"Very importantly, RIME is distinguished from drug-induced necrolysis," said Dr. Introcaso.

Terms that dermatologists are familiar with, including erythema multiforme (EM) major, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), can be problematic because they have been used in the literature to describe a spectrum of often overlapping conditions with different causes and outcomes, according to Dr. Introcaso.

"We're beginning to understand the differences in etiology, disease course, and management for patients previously described as EM major, SJS or TEN, and we're finding our nomenclature to reflect those understandings is really important."

The Relationship Between RIME and MIRM

RIME encompasses mycoplasma pneumoniae-induced rash and mucositis (MIRM), which Canavan and colleagues defined in 2015 as a specific entity of erosive mucositis and relatively mild cutaneous findings in patients with mycoplasma pneumoniae infection.[3]

"Once MIRM was defined and characterized, many physicians began to recognize that this syndrome was appearing in patients not just with *Mycoplasma pneumoniae* infection but in other respiratory illnesses. That prompted Ramien and colleagues to suggest this new term 'reactive infectious mucocutaneous eruption,' or RIME, which more accurately describes the spectrum of this condition," said Dr. Introcaso.

Who Gets RIME and Why?

According to Dr. Introcaso, both bacterial and viral respiratory pathogens have been associated with RIME. These include not only *Mycoplasma pneumoniae*, but also *Chlamydia pneumoniae*, and group A streptococcal pharyngitis as bacterial causes. Viral causes of RIME include adenovirus, human metapneumovirus, parainfluenza virus, influenza virus types A and B, and recently there have been multiple reports of the SARS-CoV-2 virus being associated with RIME.

"There aren't any large population-based studies to give us an incidence rate of RIME, but we do know that pediatric patients and younger adults are more represented in the few series that have been described. And there does seem to be a higher likelihood of men or boys being involved, with large case series describing between 54% to 62% of patients as male."

RIME Sequelae

RIME has a number of consequences, according to Dr. Introcaso.

"Although the disease tends to have a mild course, there are infrequent long-term sequelae generally due to mucosal complications, including mucosal adhesions. There is really no significant mortality that has been reported."

"However, a significant feature that has been reported with RIME is the chance for recurrence. That original 2015 review that described MIRM reported that about 8% of patients had previous episodes of similar rash or mucositis. There have also been multiple case reports of small series of patients with recurrent episodes, including some with many different infectious agents as causes of recurrence. There has been a small number of patients who have been reported to have as many as seven episodes in less than three years," she said.

Treating RIME

There is no evidence to suggest RIME patients respond to prophylactic antibiotics, but they do respond to systemic steroids when the episodes occur, according to Dr. Introcaso.

"It's important to counsel patients and families about this so they can recognize symptoms and seek appropriate care early in the course of their disease."

When faced with a patient with RIME, dermatologists should think about treatment in three general areas, according to Dr. Introcaso.

1. Supportive care

Patients need to have their pain controlled; be appropriately hydrated; and have appropriate topical medications and wound care.

2. Treatment

If a particular infection is found, it is appropriate to start antibiotic therapy—in particular, therapies for either chlamydia or mycoplasma pneumoniae. If appropriate, consider antiviral therapy, as well. Finally, consider immunomodulatory therapy.

Dr. Introcaso said she has treated her patients with prednisone or IVIg and some even with tumor necrosis factor (TNF)-alpha inhibitors.

"There are still a lot of areas of study that need to be done for appropriate treatments for these patients," she said.

3. Counseling

Patients and families do need to be counseled about recurrences of RIME, she said. ◈

DISCLOSURE:

Dr. Introcaso reports no conflicts of interest related to this topic.

"…there does seem to be a higher likelihood of men or boys being involved, with large case series describing between 54% to 62% of patients as male."

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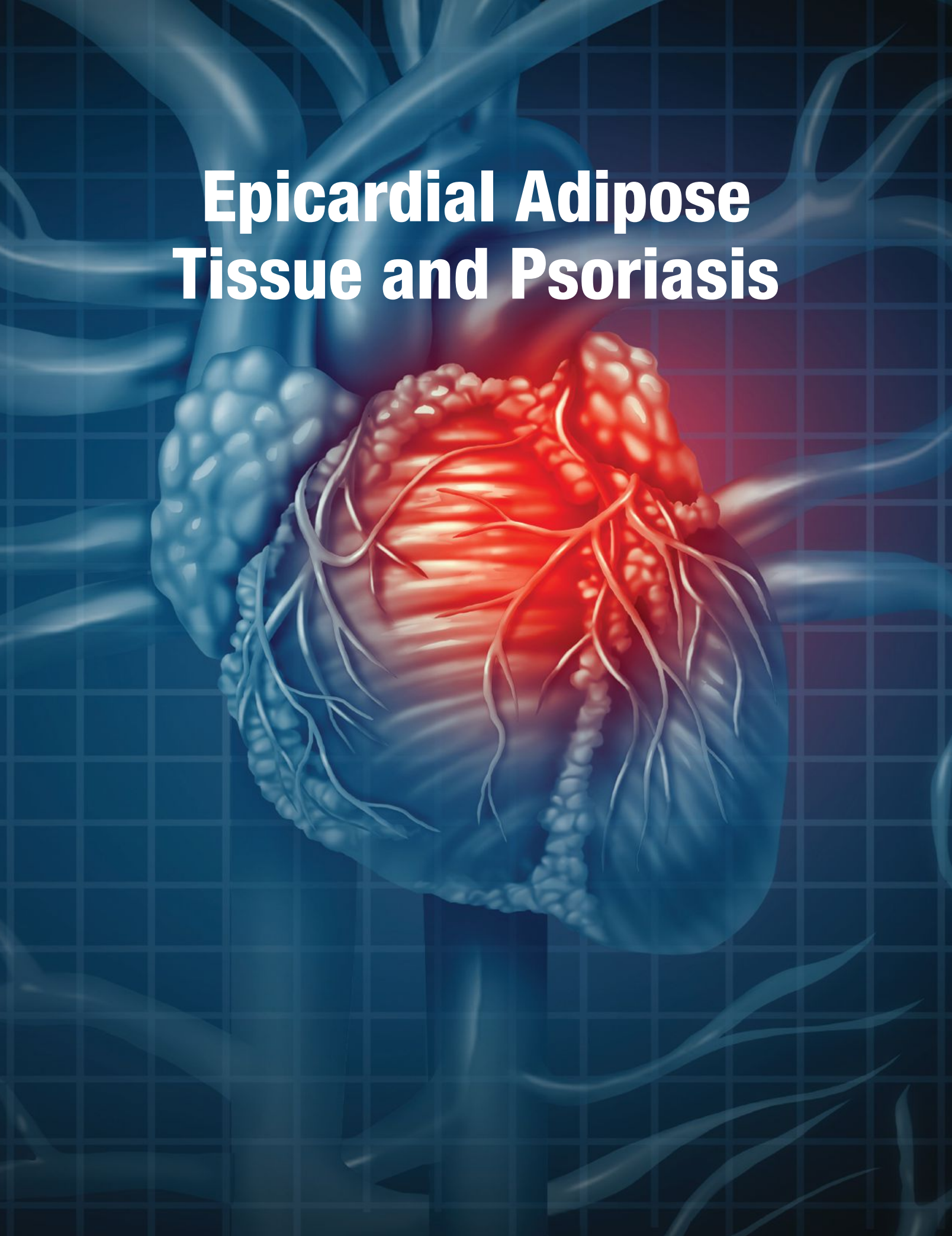
Epicardial Adipose Tissue and Psoriasis



Dr. Charles N. Ellis explains why measuring epicardial adipose tissue volume when patients with psoriasis are undergoing computed tomography cardiac imaging might be important for assessing cardiovascular risk in these patients.

"Including measurement of epicardial adipose tissue volume (EAT-V) when patients with psoriasis are undergoing computed tomography (CT) cardiac imaging should be considered because it may provide valuable additional information for assessing cardiovascular risk," said Charles N. Ellis, MD, co-lead author of a published study investigating EAT-V in psoriasis patients.[1]

"We know that patients with psoriasis have an overall increase in systemic inflammatory load that puts them at increased risk for future cardiovascular events, and therefore it is advisable to screen patients with psoriasis for cardiovascular risk factors. Although cardiac imaging is done based on clinical need and is not considered a screening test, we believe that EAT-V should be reported whenever a patient with psoriasis is undergoing a CT cardiac imaging test."

"Measurement of EAT-V is a relatively simple, safe, reproducible test that might increase our ability to identify patients who are at high risk for coronary events so that we could focus prevention efforts on patients who need it the most. Risk awareness is the first step toward prevention," he said.

What Is EAT and Why Does It Matter?

Epicardial adipose tissue lies between the myocardium and pericardium. It is metabolically active tissue that secretes proinflammatory and proatherogenic cytokines. The proximity of release of these deleterious compounds to the coronary arteries is believed to explain a documented association between EAT-V and coronary artery disease.

Although available research shows that psoriasis is associated with coronary artery disease as measured by severity of coronary artery calcification, previous studies investigating the risk of future cardiovascular events and related mortality in patients with psoriasis have yielded variable results.

"Thus there exists an unmet need for simple clinical evaluations that help predict the risk of serious cardiovascular events for patients with psoriasis," said Dr. Ellis.

EAT-V In Psoriasis Patients

Previous studies investigated EAT-V in patients with psoriasis and reported it was greater than in controls. However, most of these studies used single-location ultrasound to evaluate EAT thickness, which is only a surrogate measure of EAT-V. The studies also varied in their criteria for selecting patients with psoriasis and controls.

To further investigate the question of whether EAT-V is increased in patients with psoriasis, Dr. Ellis and colleagues conducted a cross-sectional, controlled study choosing subjects with psoriasis and controls from a convenience sample of patients seen at the University of Michigan Dermatology clinics. They focused on patients with severe chronic plaque psoriasis, defined as having >10% body surface area involvement and at least one episode of inpatient

CHARLES N. ELLIS, MD
Professor Emeritus
Department of Dermatology
University of Michigan
Ann Arbor, Michigan

"Measurement of EAT-V is a relatively simple, safe, reproducible test that might increase our ability to identify patients who are at high risk for coronary events so that we could focus prevention efforts on patients who need it the most. Risk awareness is the first step toward prevention."

therapy or systemic treatment for psoriasis. Controls had no personal or family history in first-degree relatives of psoriasis or other rheumatologic diseases.

Clinic patients were excluded from the study if they were age <18 or >55 years, had any history of heart disease, were receiving TNF-alpha inhibitor treatment, had diabetes mellitus, were pregnant, or weighed over 320 pounds.

EAT-V was determined using 3-dimensional CT, which is considered to provide accurate and reliable quantification of EAT-V. Coronary artery calcification and coronary artery plaque and stenosis were also scored. All measurements were done by an experienced cardiothoracic radiologist who had no knowledge as to whether the subject had psoriasis.

The study included 25 psoriasis patients and 16 controls; 40 participants were White.

Comparisons of demographic and cardiovascular risk factors between the patients with psoriasis and controls showed that the only statistically significant difference was for EAT-V that was greater in the psoriasis group than in controls (91 vs 70 cm^3; P =.04). There were no significant differences between the psoriasis patients and controls in either coronary artery calcification or plaque formation, likely due to selection criteria of relatively young age and absence of known heart disease.

Comparisons of demographic and cardiovascular risk factors between the patients with psoriasis and controls showed that the only statistically significant difference was for EAT-V that was greater in the psoriasis group than in controls….

Subgroup analyses of the data with patients divided by sex showed that EAT-V was statistically higher in the psoriasis patients compared to controls only among males.

Addressing the Limitations

As a small cross-sectional study performed in a convenience sample that included only patients with severe psoriasis, the research has several limitations, said Dr. Ellis.

"Because of our study's small sample size and lack of racial diversity, future areas of research include seeing if our findings are confirmed in a larger patient population and if EAT-V differs between patients with psoriasis and controls among non-Caucasians," he said.

"In addition, we believe further investigation is needed to explore whether female psoriasis patients have increased EAT-V. Although we found such a difference existed in a numerical sense, we could not prove it statistically. The explanation may lie partly in the fact that women are generally smaller and have less EAT-V than men to begin with. However, if more women are studied, I expect the results will show that EAT-V is increased in women with psoriasis just as we found in men."

"Whether elevated EAT-V is a result of increased general inflammation or is an independent cause of the increased cardiovascular risk, or both, is another opportunity for further study. We hope our colleagues in dermatology and radiology will conduct the research needed to expand on our initial findings," said Dr. Ellis.

Dr. Ellis predicts that demand for quantifying EAT-V in patients with psoriasis will increase as the significance of this metric becomes more widely recognized.

"Moreover, the rise in demand for EAT-V measurement will likely result in EAT-V measurement becoming more automated because it might motivate manufacturers of CT platforms to develop software capable of reporting the information without human input from the radiologist. However, EAT-V will not become a standalone test for prognosticating cardiovascular risk because obtaining the measurement requires patients to have clinical indications for the CT cardiac imaging that allows calculation of EAT-V," he said. ◈

By Cheryl Guttman Krader

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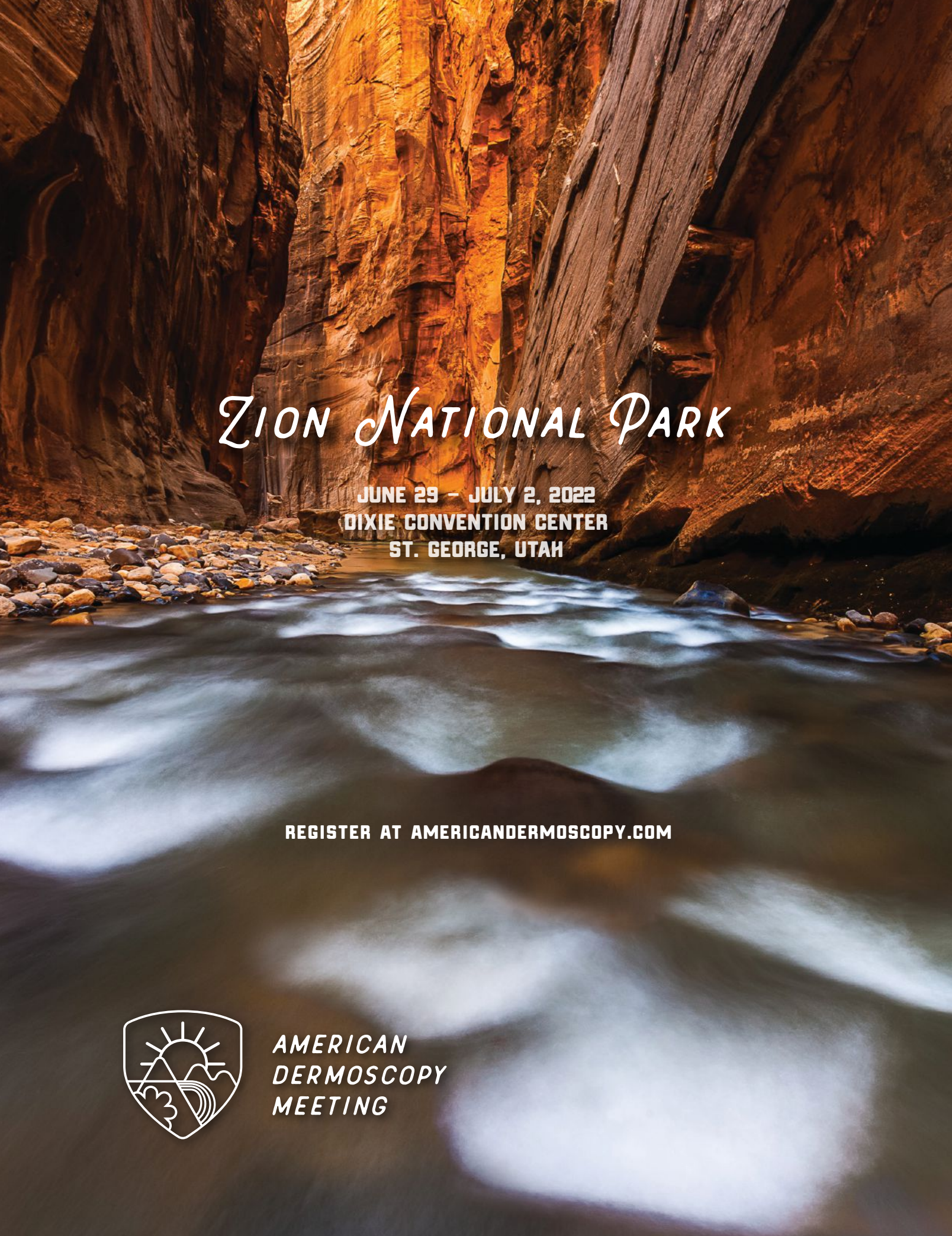

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A Novel Formulation Technology for Rosacea

By Ted Rosen, MD

TED ROSEN, MD, FAAD

Professor of Dermatology
Baylor College of Medicine
Houston, Texas

Silica microencapsulated 5% benzoyl peroxide cream (Epsolay) delivers a safe, non-irritating treatment for inflammatory (papulopustular) rosacea in adults.

The Food and Drug Administration has recently approved silica microencapsulated 5% benzoyl peroxide cream (Epsolay, Galderma) for the treatment of inflammatory (papulopustular) rosacea in adults. This product utilizes a novel technology whereby the active ingredient is incorporated within a shell composed of silica-based microcapsules. The active ingredient then slowly migrates out from the encapsulation, delivering a safe and non-irritating dose to the skin.

At trial end, inflammatory lesion count was reduced by 68.2% and 69.4% in those who received the active drug, compared to 38.3% and 46.0% among those receiving vehicle.

Epsolay approval marks the second silica-based microencapsulated agent, the first being Twyneo (benzoyl peroxide 3% and tretinoin 0.1%, Galderma), which is FDA approved for acne.

Epsolay approval was based on data derived from two parallel, double-blind, vehicle-controlled phase 3 trials (NCT 03448939 and 03564119), which evaluated the safety and efficacy of the drug in 733 subjects with moderate to severe papulopustular rosacea. Patients were randomly selected to receive either active or vehicle (placebo) once daily for 12 weeks. The co-primary endpoints were Investigator Global Assessment (IGA) score of clear or almost clear at the end of 12 weeks and the absolute reduction compared to baseline in inflammatory lesion count.

Trial results disclosed that 47.4% and 49.2% of patients in the two trials reported IGA treatment success while using microencapsulated benzoyl peroxide compared to 20.7% and 28.2% of patients treated with vehicle. At trial end, inflammatory lesion count was reduced by 68.2% and 69.4% in those who received the active drug, compared to 38.3% and 46.0% among those receiving vehicle. A significantly greater treatment effect for encapsulated benzoyl peroxide relative to vehicle was noted as early as week 2 of the trials. The pivotal trials were followed by an open-label, one-year extension trial in which 73% of Epsolay-treated patients achieved IGA success at week 52.

The most common side effects reported during the trials were application site reactions, such as erythema (2%), pain (2%), edema (1%), and pruritus (1%). Not only does this provide another therapeutic option for rosacea, it also further demonstrates the utility of this exciting novel drug formulation technology. ◈

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41st ASLMS Annual Conference on Energy-Based Medicine & Science

April 27-30, 2022

Eliot Battle, MD
is CEO and Co-Founder of Cultura Dermatology & Plastic Surgery, Washington DC

Guiding Principles for Treating SOC

Dr. Eliot Battle discusses key fundamentals that underlie the art of safely and effectively treating skin of color using energy-based devices.

https://thedermdigest.com/video/guiding-principles-for-treating-soc

"It's very important for all of us to learn how to treat skin color," said Eliot Battle, MD, who presented "Fundamentals of Laser Treatments on SOC – What Every Dermatologist Should Know," at the 41st ASLMS Annual Conference on Energy-Based Medicine & Science.

"We always hear that in 2050, over half the world is going to be brown skin. But if you look at the demographics today, in the majority of cities, we have well over 60% of skin of color patients."

As the demand for dermatologic treatment within this population of patients grows, so does the need for dermatologists to develop specific skin of color expertise, said Dr. Battle.

In pursuit of that expertise, dermatologists should follow these 5 guiding principles, he said:

1. Use the right laser or device with the appropriate wavelength for the skin color you are treating.
2. Always treat conservatively because we don't know the DNA of the patient.
3. Become an expert not only in technology, but in really understanding the nuances of skin of color.
4. Choose treatments that are proven to consistently be safe and effective on skin of color like laser hair removal, treating pigmented lesions, texture improvement, skin tightening, and body contouring.
5. Success comes from minimizing heating of the epidermis by minimizing pulse stacking, the number of passes, and fluence levels.

More Than Color

"My first take home message for this conference is, white is not white, brown is not brown."

According to Dr. Battle, if five people have the same skin color but have varying heritage (for example, African, South Asian, Japanese, Brazilian, and Italian), their skin won't react the same way.

"Every patient is unique and their skin color is

not the only consideration when treating the skin. Patients need to be treated as the unique person they are. Our skin color, although a very important criteria, is not the only one. The same skin color is different. People will react differently with lasers because our DNA is different."

Often asked how he treats African Americans, his answer is always the same—one at a time, Dr. Battle says, because each one of us has a different mixture of ethinicities and history of sun expsoure, health, and medication.

My first take home message for this conference is, white is not white, brown is not brown."

"'African American' is not an ethnicity. It's a title. Each of us is an unique mixture of African, European, Caucasian, American Indian, Latin, Mediterranean, and Asian DNA. So it's not just color. It's much more than that."

And it makes safely treating skin of color more difficult than treating lighter-skinned patients, said Dr. Battle.

"Each patient is unique and science hasn't advanced enough to understand how different DNA impacts the skin, but we know it does. We don't fully understand the genetic influences of melanin. In skin of color, melanocytes, our cells that make pigment, are more susceptible to cold and heat injury than lighter skin. And there's an increased risk of scarring with patients with skin of color."

The key to safe treatment is becoming an expert with treatments that are proven to be safe and work on skin of color, said Dr. Battle.

"If you can focus on hair removal, dark spots, texture improvement, you've got the majority of patients who are seeking your expertise. Throw in acne, body contouring, and skin tightening and you really have a large basket of treatments you can do to any patient, regardless of skin color or ethnicity."

A Word of Caution

To perform safe and effective treatments on patients with skin of color also means knowing what to avoid, said Dr. Battle.

"We're not good at treating vascular lesions, like capillaries and blood vessels, on skin of color. We're not good at resurfacing skin of color. Imagine if I took away my top layer of the skin—it's a dice roll that my skin is going to repigment evenly."

While the IPL device is great for treating lighter skinned patients, its frequency of causing side effects makes it less safe when used on darker skin, particularly Fitzpatrick skin types V and VI, said Dr. Battle.

"If I could take away the IPL device from practitioners treating skin of color, I [would] remove probably 80% of the side effects we see when patients come to us from other practices."

I also don't always trust the device treatment parameters provided by manufacturers, said Dr. Battle.

"To get FDA approval you need a couple of dozen patients, not enough data to make treatment recommendations. I generally treat more conservatively than the manufacturer's recommendations."

To safely treat skin of color with lasers and energy-based devices, "You minimize epidermal absorption of the laser light by using longer wavelengths and using non pigment- absorbing parameters like microsecond pulse durations, radio frequency devices, and ultrasound. You minimize epidermal heating by using longer wavelengths, longer pulse durations, lower fluences, and [maximizing] cooling. Heat is your enemy, cold is your friend."

And, anything that causes irritation, erythema, or edema should be minimized as those can lead to post inflammatory hyperpigmentation, said Dr. Battle.

In terms of test spots, side effects may not be apparent until 48 hours or more when treating skin color, said Dr. Battle. So when evaluationg test spots, wait at least two days prior to evalu-

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ating the patient to make sure that you're using the right parameters.

Another option is to treat so conservatively you don't need to do test spots.

Treatment Tips

Overall, safe and effective energy treatments on skin of color require some guiding principles, said Dr. Battle.

In terms of test spots, side effects may not be apparent until 48 hours or more when treating skin color….

"Again, heat is my enemy, cold is my friend. We need to cool the skin by taking heat from it. Excessive epidermal heating causes epidermal thermal injury (side effects). So we have to always keep the epidermis under 45 degrees Celsius. One way we can assist is by using longer pulse duration. The slower I pour the bucket of energy (longer pulse duration), the slower my skin absorbs it, allowing it to heat up slower, making cooling more efficient. It's easier cooling a slow heating object than a fast heating one."

Dark spots are one of the biggest reasons skin of color patients seek out aesthetic dermatologic treatments, said Dr. Battle.

"To treat dark spots [or] pigmented lesions, there are four major devices that we use consistently: fractional lasers using low energy, low density; microsecond Nd:YAG lasers; picosecond and Q-switched nanosecond lasers; and now the new kid on the block is a fractional microneedling radiofrequency device."

With fractional lasers, wavelength determines penetration depth. For water-absorbing wavelengths, the shorter the wavelength, the deeper the laser beam penetrates into the skin. The 1927 nm wavelength is shallow; 1540 nm wavelength goes much deeper, said Dr. Battle.

"My favorite fractional device is the 1540 nm wavelength, but we all can have our preferences. I also like the 1927 nm diode wavelength. It's just a matter of becoming an expert with the fractional laser you have."

For laser hair removal, the Nd:YAG is the go-to for skin of color patients, said Dr. Battle.

"We're great at laser hair removal. The Nd:YAG laser has proven over time to be the best wavelength to treat skin of color for laser hair removal. We can safely treat anyone, any color, any ethnicity with the Nd:YAG wavelength. We have to use lower fluences, longer pulse durations, maximize cooling, accurate overlapping. But again we can treat anyone."

Switching the parameters of a long-pulsed Nd:YAG to a shorter microsecond pulse duration offers treatment versatility, said Dr. Battle.

"A microsecond is 1 millionth of a second and a millisecond is 1 thousand of [a] second. So the millisecond pulse duration laser is dramatically different than the microsecond pulse duration lasers. The millisecond is the pulse duration we use for hair removal. [It's the] same device, just by changing the pulse duration, using a much shorter microsecond pulse duration, the laser light bypasses the epidermis and allows us to safely treat dermal issues. We can use it to improve texture, complexion, and even small capillaries, which makes it an effective device to improve melasma."

The new kids on the block, fractional microneedling radiofrequency devices that have been FDA approved for skin tightening, are also being used to improve texture, acne scarring, and pigmentation in skin of color patients, said Dr. Battle.

They use small pins to penetrate the skin and when treating skin of color "the pins are coated (epidermal sparing) so they're not heating the epidermis. It's only heating down deep in the dermis where the target is. You've got to be accurate with your placement. You have to minimize stacking the pulses and keep the handpiece flush to the skin. But we get consistent results improving acne scarring, texture, tightening, and complexion on skin of color." ◈

41st ASLMS Annual Conference on Energy-Based Medicine & Science

April 27-30, 2022

George J. Hruza, MD, MBA, FAAD
is Adjunct Professor of Dermatology, St. Louis University, and Candidate, Missouri State Senate, 24th District, St. Louis, Missouri

Updates on In-Office Compounding Regulations

Dr. George J. Hruza discusses proposed changes to sterile pharmaceutical compounding preparations and the ongoing advocacy efforts to ease regulations.

https://thedermdigest.com/video/updates-on-in-office-compounding-regulations

"When we anesthetize patients, we buffer the lidocaine… putting [in] a little bit of bicarbonate helps to make it less painful. And it's been used safely pretty much for at least 30 years that I've been in practice. The problem is, it's considered compounding now. And because of that, it comes under all kinds of rules and regulations," said George J. Hruza, MD, MBA, FAAD, who presented "Legal Considerations in Compounding and Mixing Drugs" at the 41st ASLMS Annual Conference.

"The issue of compounding… started with the Aspergillus meningitis outbreak from compounded corticosteroids, which led to 53 deaths and many other serious illnesses from that. And out of that arose this legislation which requires the FDA… to regulate pharmacies and anybody who compounds."

That includes dermatologists, said Dr. Hruza.

While the FDA has released regulatory guidance, the FDA is not enforcing it in physicians' offices yet, he said.

"So that one is a little bit less of a threat. The problem is that USP—United States Pharmacopeia—has made changes to chapter 797, which deals with compounding of medications, primarily in pharmacies. However, it includes compounding in any location, including physician offices."

The USP initially proposed that nonsterile pharmaceutical compounding preparations must be used within 1 hour after preparation. Advocation by dermatology organizations [has] won an extension to 4 hours, said Dr. Hruza.

"…in offices, we usually prepare buffered lidocaine in batches. And so you prepare a batch and traditionally we've been using it… for over a week. But now they say that, once this is fully implemented, you will have 4 hours to use it."

In addition to that, you'll have to label each syringe with the name of who prepared it, what's in it, and what the expiration time is, he said.

To date, appeals have prevented these chang-

The [United States Pharmacopeia] initially proposed that nonsterile pharmaceutical compounding preparations must be used within 1 hour after preparation. Advocation by dermatology organizations [has] won an extension to 4 hours.

es from becoming finalized, but because the states generally accept USP standards, changes are coming, said Dr. Hruza.

In fact, some states and facilities have already begun to implement them, he said.

"They kind of jumped the gun. Ohio actually went even before they finalized the rules. Also, if you work in a facility, like a hospital setting, then they also tend to apply those already."

In those places that are already following these expected changes in compounding standards, pharmacies are preparing buffered local anesthetic, said Dr. Hruza.

"They have it prepared in the pharmacy, and they charge them $2 for each 3 mL syringe. So that is not very practical because it gets very, very expensive."

Advocacy at Work

But changes won't be finalized without a fight, said Dr. Hruza. The American Academy of Dermatology, American Society for Dermatologic Surgery, and American College of Mohs Surgery are putting compounding standards to the test.

"What we're doing is trying to get a first-ever monograph to make those requirements—the USP requirements—less onerous..."

Specifically, the aforementioned dermatology associations will be providing the USP with the results of three tests on buffered lidocaine with epinephrine asking the USP to extend the permitted shelf-life from 4 hours to at least 12 hours.

To date, two of the three testing requirements have been met.

"If we pass the third one, which has to do with stability…, then we'll have the USP, hopefully, approve this monograph, which has never done before and will get us at least a 12-hour timeframe."

"If you prepare it according to the monograph, you'll be able to prepare lidocaine with epinephrine and buffer it and use it for the whole day. We probably won't get a whole week but certainly getting a whole day would help a lot of practices."

Other Issues

This will also concern the preparation of neuromodulators, said Dr. Hruza.

"The challenge is that if you prepare it on label… where you reconstitute with non-bacteriostatic single-use saline, then you can use it over 24 hours, but you're supposed to use it only in one patient, which for the cosmetic world is very impractical."

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But changes won't be finalized without a fight…The American Academy of Dermatology, American Society for Dermatologic Surgery, and American College of Mohs Surgery are putting compounding standards to the test.

Historically, it's been prepared with bacteriostatic saline. The benzyl alcohol content makes the injections more tolerable, said Dr. Hruza.

"The preservative is a mild anesthetic. It hurts less and, of course, using something that contains a preservative means that it can be used safely for weeks and on multiple patients."

The problem is the 4-hour rule.

"I don't have the answer for you yet because we are right now working on the [issue of] local anesthetic, and I'm hoping that once we get that through, then we can work on some of these other issues."

Another of which is the preparation of intralesional corticosteroids, said Dr. Hruza.

"Some offices that are very busy will prepare those ahead of time…. They take the full-strength triamcinolone acetonide and dilute it with bacteriostatic saline based on patient needs. This is considered compounding and therefore if you prepare it ahead of time, you will be limited to 4 hours along with the various preparation restrictions and labelling."

For now, most dermatologists don't need to change what they're doing. Wait until the guidance is finalized and until your state adopts it, said Dr. Hruza.

"…when this guidance is finally finalized, as the states take it up, we want the regulations to be promulgated by the boards of healing arts rather than pharmacy boards."

This is because we consider in-office preparation part of the practice of medicine, not pharmacy, said Dr. Hruza.

"…what's happening now in Ohio [is] the pharmacy regulators come into offices and slap heavy fines on practices that don't follow those very restrictive guidelines...."

Advocacy will continue for dermatologists and patients, said Dr. Hruza.

"Our organizations will continue fighting as it's finalized at the state level, as this is too onerous and really bad for patients."

Case in point, if practices decide not to buffer lidocaine, it's patients who lose, said Dr. Hruza.

"That patient now is going to be suffering because of this regulation. We are going to be fighting that state by state. What people can do is to support our organizations because they're fighting on their behalf." ◈

DISCLOSURES:
Dr. Hruza reports no relevant disclosures.

FOR MORE INFORMATION:
https://www.aad.org/member/advocacy/priorities/drugs/compounding

3rd Annual San Diego Dermatology Symposium
March 11-13, 2022

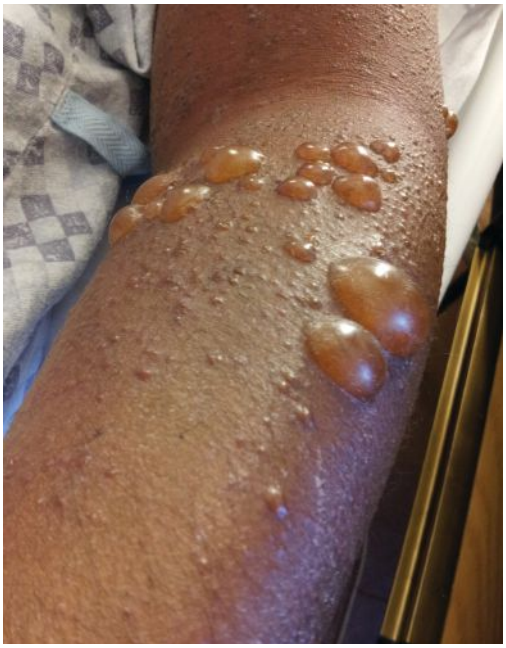
Sergei A. Grando, MD, PhD, DSc
is Distinguished Professor, Department of Dermatology, Department of Biological Chemistry, and Director, Immunobullous Clinic, University of California Irvine, Irvine, California

Multidrug Protocol Shown to Cure Pemphigus, Pemphigoid

Dr. Sergei Grando shares his multidrug protocol shown to offer potential cure for the majority of pemphigus and pemphigoid patients.

https://thedermdigest.com/podcast/multidrug-protocol-may-cure-pemphigus-pemphigoid

"Before corticosteroids were introduced in the 1950s, the mortality from pemphigus was 50% within 2.5 years and 100% within 5 years of the disease. …steroids changed the entire field, so patients no longer died from this disease if they were treated in a timely manner before they developed sepsis and other complications," said Sergei A. Grando, MD, PhD, DSc, who presented "Pemphigus and Pemphigoid," during the 3rd Annual San Diego Dermatology Symposium.



But steroids alone far from solve the problem, said Dr. Grando, who directs one of the largest centers of excellence in the U.S. treating patients with pemphigus and pemphigoid.

"Another problem is that prednisone, instead of being a friend, becomes a foe. Doctors who don't have experience treating these patients often either overtreat patients with too much for too long, leading to serious side effects, or they treat [with] too little for a short time and patients relapse."

"That's why, unfortunately, mortality to date, which is about 10% on average, stems from complications from treatment rather than from the disease itself," he said.

3 Treatment Goals

Pemphigus and pemphigoid are similar in that there are three potential targets for therapy,

> "…unfortunately, mortality to date, which is about 10% on average, stems from complications from treatment rather than from the disease itself."

according to Dr. Grando.

1. Increase resistance to autoantibodies
2. Eliminate autoantibodies
3. Prevent autoantibody production

"First of all, there is resistance of skin cells, or keratinocytes, to autoantibodies. It's not uncommon to have patients with antibodies in the system but no lesions. That means that whatever the damage the antibodies can produce is not sufficient for keratinocytes to detach, which is natural resistance. So, one way to help patients is to increase resistance to autoantibodies."

"The second is to eliminate autoantibodies. Because if you increase resistance without eliminating autoantibodies they will accumulate and, at some point, they will overcome the natural resistance."

"The third component is to prevent autoantibody production. If you don't keep eliminating autoantibody-producing cells, they will be still producing."

The currently approved FDA protocol for treatment includes rituximab plus prednisone, said Dr. Grando.[1]

"In this protocol 32% pemphigus vulgaris patients who were in clinical remission off therapy relapsed within 5 years after treatment,[1,2] and 50% relapsed within approximately 2 years after discontinuation of treatment," said Dr. Grando.[3]

But in the multidrug protocol that Dr. Grando documented in an article published in the *International Journal of Dermatology*, only 12% of patients who were in clinical remission relapsed within 5 years.[4]

"That paper was not part of any clinical trial. I am the single author. And that paper summarizes my life-long experience with treating patients with this pathology," said Dr. Grando.

The paper summarizes clinical outcomes of 123 pemphigus patients treated with the 2-plus year multidrug protocol combining intravenous immunoglobulin (IVIG), an immunosuppressive cytotoxic drug and mitochondrion-protecting drugs from 2007 to 2017.

"The overall complete remission rate of all drugs was 100%, with 12% overall relapse rate. No patients had more than a single relapse," writes Dr. Grando.

The multidrug IVIG regimen achieved three principal treatment objectives: rapid control of pemphigus symptoms, stable disease remission, and prevention of flares, concluded Dr. Grando.

"These are the components of the multidrug protocol I designed."

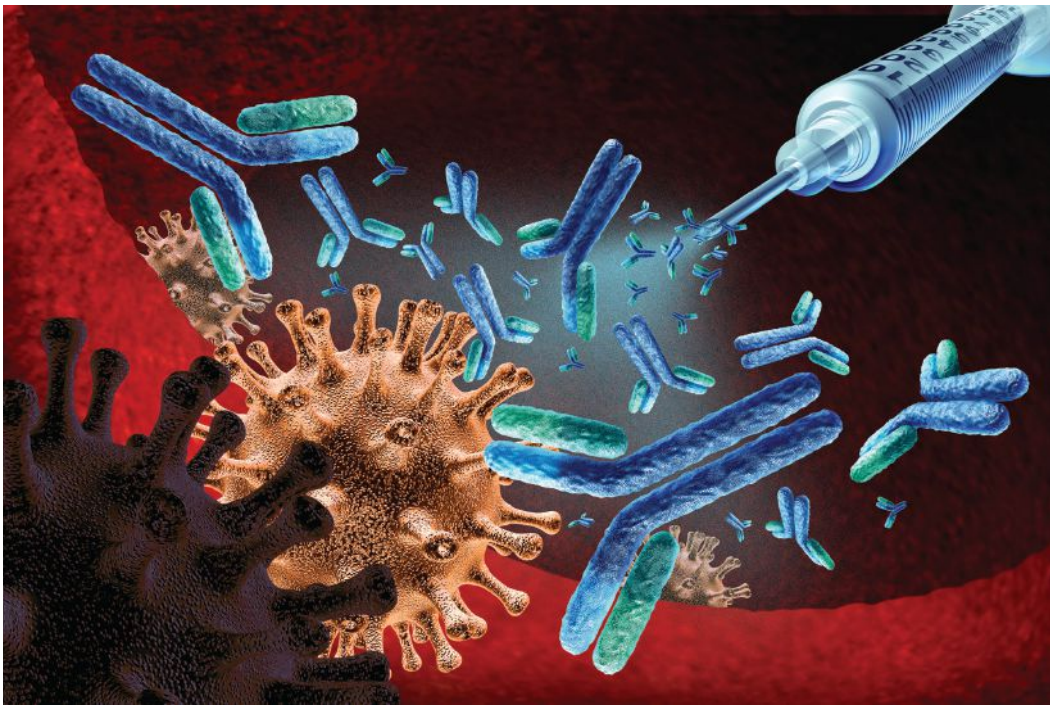
"To achieve resistance of keratinocytes to autoantibodies, we use systemic corticosteroids (prednisone taper) and mitochondrion protection with niacinamide (also known as nicotinamide) plus tetracycline-type medications. Then we need to eliminate autoantibodies with IVIG. In the past we would eliminate the autoantibodies by using plasmapheresis or plasma exchange, which is no longer reasonable to use because of the price and the need for hospitalization."

Finally, the protocol prevents autoantibody production with the use of cytotoxic immunosuppression.

Keratinocyte Resistance to Autoantibodies

Corticosteroids protect keratinocytes from autoantibody attack, according to Dr. Grando, who cited a study published in 2004 in the *Journal of Biological Chemistry*.[5]

"Methylprednisolone increased the protein levels of E-cadherin and desmoglein (Dsg) 1 and Dsg 3 by 300%, 180%, and 40% respectively. There is gene expression targeted by steroids that leads to upregulation of adhesion molecules, so antibodies are present but keratinocytes acquire higher resistance," he said.



The multidrug IVIG regimen achieved three principal treatment objectives: rapid control of pemphigus symptoms, stable disease remission, and prevention of flares.

"Corticosteroids need to be handled with care. Walter F. Lever, MD, published a very useful manual Lever WF. *Pemphigus and Pemphigoid*. Springfield: Charles C. Thomas, 1965, in which he gives very specific recommendations that prednisone should be started at 1 mg/kg/day. Use that dose for about 10 days or so, and if it doesn't start to heal existing erosions or if patients develop new lesions, go up by 30% until the disease is under full control. Patients should have no lesions, epithelialization of existing erosions, and negative Nikolskiy sign. Then you can start tapering in a logarithmic fashion by about 25% of the current dose every 2 to 3 weeks."

Dr. Grando then described the mitochondria's role and use of minocycline and niacinamide as part of the protocol.[6]

"Mitochondrial damage has been demonstrated … in both pemphigus and pemphigoid. We and other authors demonstrated empirically that tetracyclines in combination with niacinamide can protect the mitochondria," said Dr. Grando.

Autoantibody Elimination, Prevention

IVIG saturates the FcRn receptors, which protect immunoglobulin G (IgG) molecules' degradation inside the cell.[7] Since both disease-specific and normal IgG antibodies are eliminated but only normal antibodies are replenished from donors' IgG batches, there is selective drop in the serum level of autoantibodies, he said.

"Selective elimination of autoantibodies may lead to a 'rebound effect' [or flare] due to stimulation of autoantibody producing cells. There is a way to address that problem …with coadministration of a cytotoxic immunosuppressor. It was shown that combining IVIG with a cytotoxic immunosuppressor prevents compensatory overproduction of pathogenic autoantibodies triggered via negative feedback by their selective elimination."[8]

"You start IVIG usually monthly at 2 g/kg/month for 4 to 5 day-long cycles for about a year. Then, 6 months after systemic steroids have been discontinued, you continue IVIG on a taper

But in the multidrug protocol that Dr. Grando documented… only 12% of patients who were in clinical remission relapsed within 5 years.

schedule—first with one cycle at 2 months for 6 months and then one in 3 months, twice. And this goes at the background of the use of an immunosuppressant cytotoxic drug, minocycline (or doxycycline), and niacinamide. The duration of the multidrug treatment is usually about 2 years," said Dr. Grando.

"There is an alternative protocol where you use rituximab at 375 mg/m^2 body surface for a total of 10 times during first 24 weeks of treatment. You use rituximab weekly x 3 for the first 2 months, then once a month for an additional 4 months. That's along with IVIG 2 g/kg/month. All this at the background of minocycline and niacinamide. Once we finish the 6 months of treatment with rituximab, then we go to an oral cytotoxic immunosuppressor, so again the treatment is for two years."

Outcomes are better with the multidrug protocol compared to treatment with only prednisone and rituximab because of the latter treatment's inability to selectively suppress production of pathogenic autoantibodies, according to Dr. Grando.

"Rituximab targets all CD20 positive B cells regardless of their relevance to pemphigus vulgaris. The targeting of a disease-specific B cell clone occurs purely by chance and the majority of B cell populations repopulate after treatment with rituximab. Unfortunately, those treated with rituximab usually have a flare about once a year."

"But if you use IVIG in the multidrug protocol, the IVIG selectively and predictably eliminates pathogenic antibodies because both normal and pathogenic antibodies are cleared at the same rate, and normal antibodies are replenished by normal IgGs in IVIG batches," he said.

Treatment Duration Key

Maintenance with IVIG and an immunosuppressor should be continued for at least 2 years in expectation that the critical mass of autoreactive plasma cells dies off during this timeframe, according to Dr. Grando.

"If you keep patients lesion free for that long a period of time, there is scientific evidence to suggest that critical mass of autoreactive plasma cells will die off during this timeframe. If patients have a flare, they kind of reset the clock of possible cure …. Then you have to wait for another two years before you can expect stable remission off drugs. And that's why the current approach with prednisone and rituximab is not really helpful [for a] real chance for cure." ◈

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DISCLOSURE:

Dr. Grando reports no conflicts of interest.

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PART 3 OF *THE DERMATOLOGY DIGEST*'S 3-PART JAK INHIBITOR SERIES

JAK Inhibitors and AD: Why, When, and How

Drs. George Martin and Ted Rosen talk candidly about why JAK inhibitors are important in the treatment of atopic dermatitis (AD), when dermatologists should consider using them, and how to safely mitigate risks and side effects while effectively treating AD patients with these powerful, "revolutionary" medications.

https://thedermdigest.com/video/jak-inhibitors-and-ad-why-when-and-how

"Why do we need JAK inhibitors to treat atopic dermatitis? Like so many things, we've had treatments before. This isn't a disease that has no treatments at all, but I think we can always do better. That's the goal, one way or another, with something that's more efficacious, safer, or better," said Ted Rosen, MD, FAAD.

AD treatments are experiencing a revolution and the addition of JAK inhibitors is part of that, according to Dr. Rosen.

"Think about what we did for atopic dermatitis that required systemic therapy in the past. Cyclosporin was my favorite rescue drug. But you know there is a time limit on it, there is the potential for hypertension, renal toxicity. Then we have things like azathioprine. About one in three patients that get started on that drug stop it because of side effects. It's a great drug but with serious problems. Methotrexate [has] a bunch of Black Box warnings. It can be a difficult drug to give, and tolerance is not so great. We could use mycophenolate. I love mycophenolate mofetil, but it's slow. It takes forever to work. And because it's slow and may be a little safer, it's not as efficacious."

There's always phototherapy, but then there are the issues of convenience, travel time, expense and more, according to Dr. Rosen.

"Yes, all those therapies work, but all of them have significant downsides and all of them sometimes didn't work. Between side effects, downsides, and inconvenience, we needed other drugs."

That ushered a revolution in treatment, namely dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals), according to George Martin, MD.

"The introduction of dupilumab for atopic dermatitis clearly was a total gamechanger and enabled us to treat atopic dermatitis. Now in the space of two months, December to January, we had the introduction of an IL-13 specific monoclonal antibody in tralokinumab (Adbry, LEO Pharma). And in January we got two Janus Kinas (JAK) 1 inhibitors, abrocitinib (Cibinqo, Pfizer) and upadacitinib (Rinvoq, Abbvie) that are absolutely amazing. Much to my surprise,

based on comparative data, the two JAK 1 inhibitors are as good or better than dupilumab, which has heretofore been our gold standard."

Dupilumab is a good drug. It has been relatively well accepted by dermatologists, it is a pretty safe drug and doesn't really require lab testing, according to Dr. Rosen.

"I think its downside, if you want to call it that, is its efficacy. … we could do better and in fact have done just that."

Nuances of JAK Inhibitors

There are four JAK inhibitors: JAK 1, 2 and 3 and TYK 2. [For more on those see parts 1 and 2 of this series in the April and May issues of *The Dermatology Digest* at https://thedermdigest.com/.] Different JAK inhibitors block different JAKs and affect different cytokines. Interestingly, the Janus kinas/signal transducer and activator of transcription (JAK/STAT) pathway controls over 50 inflammatory and immunomodulating signals in dermatology, according to Dr. Martin.

"As we think specifically about AD and look at the different JAKs that we can block, blocking JAK 1 makes total sense because JAK 1 is the signal transduction molecule for important cytokines like IL-13, and IL-4. We know dupilumab targets IL-4 and IL-13 and tralokinumab targets IL-13. Additionally, blocking JAK 1 inhibits thymic stromal lymphopoietin (TSLP) which is released by keratinocytes and recruits inflammatory T cells, IL-31 which is really important in itch, and other cytokines that really are very important in atopic dermatitis."

The Tofacitinib Legacy and Black Box Warning

Today's Black Box warning on all JAK inhibitors is based on a year-long study called the ORAL Surveillance study,[1] which involved only tofacitinib (Xeljanz, Pfizer), according to Dr. Rosen.

"You have to understand that tofacitinib at therapeutic doses is sort of a pan JAK inhibitor. It's primarily JAK 1 and 3 but it can block all. Its side effects are not necessarily generalizable to other JAK inhibitors that are more selective in which JAKs they block."

And subjects in the ORAL Surveillance study are not representative of most AD patients. Most subjects in that study were older than 50 years, had rheumatoid arthritis (a T helper 1 (Th1) cytokine driven disease versus AD which is driven by Th2), and at least one pre-existing cardiovascular risk factor, according to Dr. Rosen.

"That is a study that is destined to give you results that are somewhat negative and a lot of that is then translated into an expanded Black Box warning. This does not necessarily apply to giving a non-tofacitinib JAK inhibitor to a 28-year-old with atopic dermatitis."

Among the things that ended up in the Black Box warning in large part because of that study included increased all-cause mortality; increased major adverse cardiovascular events (MACE), like myocardial infarction (MI), stroke; increased risk of cancer; increased risk of infection; and increased risks of deep venous thrombosis (DVT), pulmonary embolism (PE), even arterial thrombosis, according to Dr. Rosen.

"Think about that. Some of my patients actually read that package insert and they see these horrible Black Box warnings right at the start, based upon this study that wasn't necessarily applicable to the JAK inhibitor that they just picked up at the drug store, and it really sounds scary."

Putting Things in Perspective

The Black Box warning on JAK inhibitors does not necessarily apply to AD patients. And it is the dermatologist's job to put things in proper context for patients, according to Dr. Rosen.

Rheumatologists, according to Dr. Martin, use tofacitinib and other JAK inhibitors to treat rheumatoid arthritis (RA), psoriatic arthritis, ulcerative colitis, and ankylosing spondylitis. Most of the safety data has come from the use of tofacitinib for over a decade in the RA population, a disease state inherently prone to strokes,

The Black Box warning on JAK inhibitors does not necessarily apply to AD patients. And it is the dermatologist's job to put things in proper context for patients, according to Dr. Rosen.

DVTs, lymphoma and MACE events, he said.

The reality for dermatologists is that JAK inhibitors have the potential to revolutionize what dermatologists do, according to Dr. Rosen.

"We need to approach these drugs very thoughtfully."

That's where the data in dermatology comes in, according to Dr. Martin. In Phase 3 comparator trials with dupilumab,[2] upadacitinib outperformed dupilumab for every measure, including Eczema Area and Severity Index (EASI) 75, 90 and 100, as well as itch reduction.

In Phase 3 comparator trials with dupilumab, upadacitinib outperformed dupilumab for every measure, including Eczema Area and Severity Index (EASI) 75, 90 and 100, as well as itch reduction.

"And abrocitinib, even though not powered, the 200 mg dose taken once daily was as effective or more effective than dupilumab."

Abrocitinib is approved for 18 years and older and upadacitinib for 12 years and older. Dupilumab is approved for patients 6 years and older, while tralokinumab is approved for AD patients age 18 and older, according to Dr. Martin.

Mitigating Risk

According to Dr. Martin, when it comes to safely prescribing JAK inhibitors to AD patients, there are several important considerations: patient age and drug delivery; sex of the patient, with childbearing considerations; as well as risks of cardiovascular/MACE/ mortality, cancer, DVT/PE, serious infections, and renal/ hepatic impairment.

Age is an important consideration when deciding whether to recommend one of the JAK inhibitors or one of the two available biologic therapies, according to Dr. Rosen.

"We need to stay in the guidelines for age. You probably wouldn't get insurance to pay for it anyhow."

Then there is the issue of drug delivery. The biologic therapies are injected; the JAK inhibitors are pills, said Dr. Rosen.

"I used to think when the biologics came out for psoriasis the injections would be very difficult. Now with self-injectors it's easy as pie. I think ultimately anybody can be taught to give themselves injections. But there are some people who are incredibly needle phobic."

The potential for pregnancy is a concern, according to Dr. Martin.

"We know from the data that half of pregnancies are unplanned, and most women do not know they are pregnant until 4 to 6 weeks into it. We also know that JAK inhibitors cross the placenta and that biologics take about until week 13, at which point they become transported across the placenta. So, we have a little leeway until about week 13 with the biologics."

The message there is to have a frank discussion with patients that they must not be pregnant when they start JAK inhibitors and have to be on a reliable form of birth control while taking JAK inhibitors, according to Dr. Martin.

Dupilumab may be a slightly different story, although the data is not yet clear, said Dr. Martin.

"The data with the biologics, particularly the longest standing biologic dupilumab, does not offer tremendous guidance but at the same time … data with pregnant monkeys on dupilumab showed no impact on pregnancy, and the pregnancy registry data so far looks pretty favorable as far as dupilumab."

"With regard to JAK inhibitors, our longest standing registry data comes from tofacitinib. And when I really began to do a deep dive on it, I was perplexed because I was getting mixed messages. When you look at the data on tofacitinib, what you find is that half the births or more do just fine and there are about a quarter that elect to terminate the pregnancies. But when you look at the background, the baseline incidence of severe birth deformities doesn't appear to be that much different at about 2 to 3% and miscarriages at about 15% to 20%."

The 2020 American College of Rheumatology guidelines "Reproductive Health in Rheumatic

and Musculoskeletal Disease," does not provide guidelines on whether to administer JAK inhibitors during pregnancy because of a lack of evidence regarding the use and safety of tofacitinib during pregnancy, according to Dr. Martin.

"I tell my patients: 'Don't get pregnant while on this medication. We don't have long-term pregnancy data.'"

Dr. Rosen said that since even reliable forms of contraception have been known to fail, it is important that dermatologists document those conversations and consider having patients sign a patient consent form that they understand the risks.

As for the potential risks of MACE, Dr. Rosen said dermatologists should think about who is at risk at baseline, which includes patients who are obese, have hyperlipidemia, have had past MACE events, or have a stent.

"Whether you believe that the ORAL study applies to other JAK inhibitors or not, people who are at already high cardiovascular risk (unless your back is against the wall) should not receive JAK inhibitors," said Dr. Rosen.

Patients at baseline risk for thrombotic events include those who are very sedentary, people on estrogen dominant hormones, smokers (who also are at increased risk for MACE and cancer), and those who have had thrombotic events, according to Dr. Rosen.

"Those would be the patients I would seriously consider not giving a JAK inhibitor to, or I would have them sign an informed consent if I do."

Determining a patient's cancer risk involves common sense, according to Dr. Rosen.

"I do the same with the biologic drugs, even though the data over the years has not shown a terrible increased risk of cancer, but someone who has had breast, prostate or lung cancer two years ago, I might consider not using JAK inhibitors. Someone who had lymphoma two years ago, I might consider not using a JAK inhibitor. A strong genetic predisposition for cancer … I might think twice about using these drugs, and if I did, I would certainly get my informed consent."

Patients at serious risk for infection are another group that may not be candidates for JAK inhibitors, according to Dr. Rosen.

"Again, common sense. If someone has an infection, that's not the time to start a JAK inhibitor."

The infections to worry most about are things like hepatitis B, hepatitis C, and tuberculosis, said Dr. Rosen.

"From the outset, we rule out these kinds of chronic, smoldering, possibly asymptomatic infections that may be latent infections, but they're not gone. You're going to have to get lab work anyhow, so looking for those chronic infections I think is reasonable."

Early studies on tofacitinib described a zoster signal, which brings up the issue of vaccinations for people who are going to take JAK inhibitors, according to Dr. Martin.

To address zoster and other vaccines, including for influenza, pneumococcal, and COVID-19, Dr. Rosen said dermatologists should recommend patients get the live vaccines before starting JAK inhibitors.

"Maybe talk to their primary care provider to make sure their vaccinations are up to date. We do not give live vaccinations to anybody who is on a JAK inhibitor. It's not dangerous. it's just that the vaccine won't work because the patient doesn't get an immune response to the vaccine."

Dr. Martin studied cytokines upregulated in the SARS-CoV-2 vaccine platforms and found that indeed the vaccines upregulated tumor necrosis factor (TNF), IL-6 and interferon gamma.

"It turns out IL-4 and IL-13 were not upregulated so there is not an issue with IL-13 and IL-4αR monoclonal antibodies in COVID vaccinations. With JAK 1 and 2 inhibition,

"We do not give live vaccinations to anybody who is on a JAK inhibitor. It's not dangerous. it's just that the vaccine won't work because the patient doesn't get an immune response to the vaccine."

you may suppress vaccine uptake and antibody formation particularly in older individuals and withholding JAK therapy for a week after immunization is currently recommended," said Dr. Martin.[3]

It's also important that dermatologists prescribe JAK inhibitors to patients who have working kidneys and livers, according to Dr. Rosen.

He does that by ordering laboratory blood draws, which the doctors said they check at regular intervals when patients are on JAK inhibitors.

"I don't want to start a JAK inhibitor in somebody who is already anemic, has thrombocytopenia or leukopenia. I want to know that they have a decent CBC. A comprehensive metabolic panel is reasonable because you want to make sure they have good renal and hepatic function and that there isn't some hidden thing. I also want to know they are not pregnant to start with," said Dr. Rosen.

Checking Labs

Dr. Martin agrees that JAK inhibitor patients should have baseline comprehensive testing for peace of mind. At 3 to 4 months out, he rechecks the CBC and comprehensive metabolic profile (CMP).

"If everything is still good and I have a fairly healthy individual, I'm probably good for a year unless the patient complains that something has changed. We follow patients [in the office] on these drugs usually every 6 months—first seeing them at 3 months to see how they're doing."

To limit his test taking and documenting, Dr. Rosen asks patients when they are seeing their primary care doctor.

"If they're seeing their primary care doctor six months after I do the draw, that's good. I'll ask to see those results. That's one less thing you have to do and keep track of."

Built-in Dose Adjustments

With upadacitinib, dermatologists can start with 15 mg QD and go up to 30 mg QD. With abrocitinib, they can go from 100 mg QD to 200 mg QD, according to Dr. Rosen.

"So, you can change those doses and there is increased efficacy with the higher doses. We have dose adjustment built in, but then we also have to think about the increased risk and have that discussion with the patient about how we haven't quite gotten to where we want even though this is a great drug, let's go up on the dose."

Bottom Line

Dr. Martin calls the two biologics and two JAK inhibitors for AD "an embarrassment of riches."

But a confusing, complex one at that.

"We're not talking about methotrexate, cyclosporin, azathioprine, and mycophenolate mofetil anymore, and we're not talking about dragging people in for phototherapy. These are more convenient and are as or more efficacious than we had before," said Dr. Rosen.

Dermatologists should offer AD patients who are candidates for systemic therapy an objective presentation, allowing patients to them guide them, according to Dr. Rosen.

"Give these new drugs their due. Remember they're good. They are potent, powerful and outdo the biologic drugs. It's a little more complicated for everybody but do not go into this thinking: 'Oh, we've got new drugs but they're oh so scary.' That's really the message I hope you take away from this discussion." ◈

DISCLOSURES:

Dr. Martin is on the Scientific Advisory Board of: Bristol Meyers Squibb (BMS), DUSA/SUN, AbbVie, Ortho/Bausch Health, Galderma, Pfizer, LEO, Janssen, Horizon, UCB, Trevi, Almirall, Dermavent, Incyte, Lilly, EVELO, and Sanofi/Regeneron. He is a consultant for: Bristol Meyers Squibb, DUSA/SUN, AbbVie, Ortho/Bausch Health, Galderma, Pfizer, LEO, UCB, Trevi, Almirall, Lilly, Arcutis, Dermavent, and EVELO. And is a speaker for: UCB, Almirall, LEO, Incyte, Dermavent, BMS, and Sanofi/Regeneron.

Dr. Rosen reports no disclosures related to this topic.

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Michael Ming, MD, FAAD
is Associate Professor of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Preemptive Interventions for Malignant Melanoma

Dr. Michael Ming discusses current and future treatment possibilities for prolonging survival in patients with early stage malignant melanoma.

https://thedermdigest.com/video/preemptive-interventions-for-malignant-melanoma

"…for a long period of time, we really didn't have [melanoma] treatment options that prolonged survival for people with metastatic disease. It's fairly recent that we have treatment options that impact survival for patients who have melanoma that has spread beyond the skin to other organs," said Michael Ming, MD, FAAD, who directed the session "The Changing Landscape of Early-Stage Melanoma Management" at the 2022 American Academy of Dermatology (AAD) Annual Meeting.

"In 2011, which was only 11 years ago, we had the first FDA-approved treatment for metastatic melanoma, ipilimumab (Yervoy, Bristol Myers Squibb), that was shown to be effective in prolonging survival as opposed to just shrinking a tumor or making a patient temporarily feel better. Since then, there has been an explosion of options, which is really wonderful."

According to Dr. Ming, there are a dozen different options available today that can effectively help to prolong survival in the metastatic melanoma population.

"But up until extremely recently, those [treatment options] were only available for patients who already had metastatic disease. In order to receive these treatments, patients had to have a melanoma that had already gone beyond the skin into the lymph nodes or to the visceral organs."

But, said Dr. Ming, what if we could intervene sooner in patients with melanoma who are at high risk for metastatic disease, before it spreads? Great minds—and a few trials—are currently at work on this, he said.

"One of the first trials that examined the effectiveness of medical intervention for patients who, as far as we know, still have melanoma confined only to the skin, just came out in the fall of 2021."

The study looked at pembrolizumab (Keytruda, Merck), an immunotherapy FDA-approved since 2014 for patients with metastatic melanoma, in 976 patients. Preliminary, 1-year trial results were presented at the European Society for Medical Oncology (ESMO) Congress in 2021.

> It's really an exciting time because there are a lot of avenues that are being investigated, and I think the way we think about patients in the Stage IIB/IIC group now compared to the way we'll think about them five years from now may be very, very different."

… there are a dozen different options available today that can effectively help to prolong survival in the metastatic melanoma population.

"The question is this: [For] patients who are very high risk—patients who are AJCC Stage IIB or IIC (patients who either have melanomas that are more than 2 mm with ulceration or more than 4 mm regardless of whether they have ulceration), if you intervene earlier, will [they] actually do better?"

It's an important question because those patients with a negative sentinel node procedure and an initial workup that shows no evidence of metastatic disease have about a 10-year survival rate of 80%, which means about 20% of such patients will die over that time span, said Dr. Ming.

"Rather than waiting until we have evidence of a problem, why don't we see if we can intervene earlier?"

From that 1-year data, researchers found a 7% difference in recurrence-free survival, which was statistically significant, said Dr. Ming.

"So 90% of the people who received pembrolizumab had no recurrence for a year. And 83% of the patients who did not get the medication… had a recurrence."

Based on these data, the FDA approved pembrolizumab for stage IIB/IIC patients in December 2021, said Dr. Ming.

"That's a big change because now those patients—who, again, as far as we know after the initial workup don't have an issue—are eligible for treatment."

Because there are side effects to consider, prescribing pembrolizumab warrants careful consideration and a discussion with the patient about whether it is the right option for them, said Dr. Ming.

"They should either see an oncologist or a pigmented lesion specialist or somebody who [will] discuss that with them."

According to Dr. Ming, there are other ongoing trials as well, though he isn't aware of the release of any preliminary results. One is investigating nivolumab (Opdivo, Bristol Myers Squibb), a similar drug to pembrolizumab, for early intervention of melanoma in high-risk patients. Another explores whether targeted therapy with encorafenib (Braftovi, Pfizer) and binimetinib (Mektovi, Pfizer) would be helpful for patients with disease confined only to the skin.

"There's also a trial going on at Penn, where I work, which is looking at even an earlier step."

That step is treating melanoma patients with pembrolizumab prior to a sentinel lymph node procedure, said Dr. Ming.

"The idea is that if they have tumor in the sentinel node at the time they are receiving immunotherapy, then maybe it will prime the immune system in some way. So having the antigen present might actually be helpful in terms of response."

This trial is also ongoing without preliminary results available yet.

"These three additional trials plus the additional information from that first trial (because again, there's no actual full manuscript from that trial—it's still ongoing as well)… will provide us a lot of information. It's really an exciting time because there are a lot of avenues that are being investigated, and I think the way we think about patients in the Stage IIB/IIC group now compared to the way we'll think about them five years from now may be very, very different." ◈

Large, Painless, Thin-walled Blister Ruptures, Then Many Smaller Bullae Appear

By Ted Rosen, MD, FAAD

TED ROSEN, MD, FAAD
Professor of Dermatology
Baylor College of Medicine
Houston, Texas

CASE HISTORY

A 78-year-old male being treated for rheumatoid arthritis with adalimumab and low dose prednisone (10 mg daily) developed a solitary painless red plaque on the abdomen, which, in 12 hours, evolved into an eschar.

At that point, the patient felt unwell and became febrile and reported to the emergency department. The lesion was recognized as ecthyma gangrenosum, typically (about 75%) associated with pseudomonas septicemia. He was admitted and started on appropriate intravenous antibiotic therapy (piperacillin/tazobactam and levofloxacin). This intravenous regimen was continued for two weeks.

On day 12, however, the patient developed a large, painless, thin-walled blister on his left shin. This initial blister ruptured but was followed by the appearance of multiple smaller tense bullae close to the site of first lesion. (Figure 1)

Dermatology was then consulted for the first time and noted that both legs were grossly swollen and erythematous. Prior chart notes had commented on pre-existing venous insufficiency and associated stasis dermatitis. A biopsy was done on one of the small bullae and revealed a subepidermal split with a paucicellular lymphocytic perivascular infiltrate and widened spaces between collagen bundles. All tissue stains for microorganisms were negative.

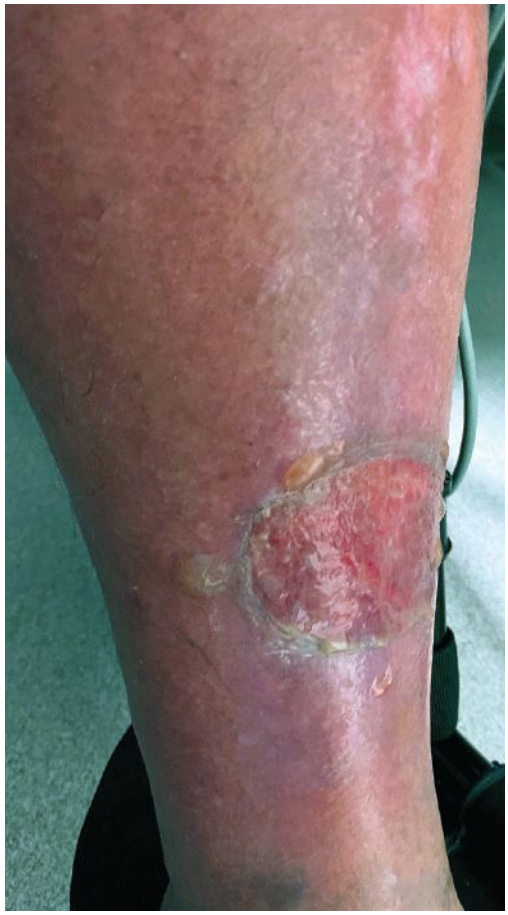


Figure 1.

What is your diagnosis?

For more on this case, turn to page 48 ▸

continued from page 47

LARGE, PAINLESS, THIN-WALLED BLISTER RUPTURES, THEN MANY SMALLER BULLAE APPEAR

DISCUSSION

The patient has fairly classic edema bullae, also known as edema blisters.

This non-infectious, non-immunologic cause of blister formation occurs mostly in elderly, immobile individuals during periods of increased interstitial pressure.

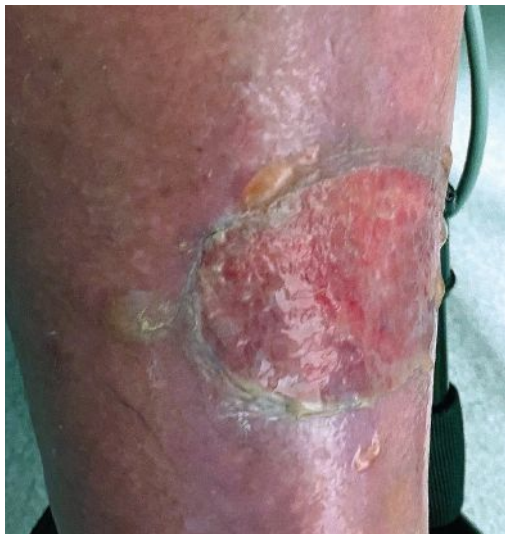
Edema bullae are medium to large sized, with a thin roof which frequently breaks.

The etiopathogenesis of this phenomenon is when capillary filtration develops too rapidly for compensatory lymphatic drainage.

Underlying causes for this physical phenomenon include hepatic, renal, or cardiac failure or simple fluid overload (often iatrogenic), particularly in the setting of venous insufficiency. This particular patient had a history of long-standing venous insufficiency and stasis dermatitis, and then was subject to intravenous fluids for two weeks. This appropriate but unfortunate fluid overload led to such intense peripheral edema that bullae formation took place.

Treatment of edema bullae is directed towards reducing the fluid overload and tissue edema. Stopping the intravenous fluid as soon as possible was a critical step. Elevation of the affected extremity was another maneuver utilized to facilitate removal of edema fluid from the blister-bearing site.

Administration of diuretics may also be considered. Lymphatic obstruction may be sought when there is no prior history of venous disease, and any organ failure which is associated with edema should be corrected as feasible.



The key point is to recognize this relatively benign condition for what it is, initiate steps to reduce edema fluid, and avoid treatments for immunobullous disorders. A biopsy may certainly help distinguish between edema bullae and blisters due to pemphigus and pemphigoid, although biopsy of an edematous extremity may lead to a slowly healing wound. ◈

RECOMMENDED READING:

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