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THE Dermatology® Digest

Vol. 3, No. 1 | January 2022

Oncodermatology Improves Quality of Life

- Vitiligo Treatment Updates
- Psoriasis During Pregnancy
- Tips for Leg Vein Treatment

EDUCATIONAL • INTERACTIVE • AUTHORITATIVE

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

THE ONE-OF-A-KIND
TOPICAL JAK INHIBITOR

NEW 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 1249 adult and adolescent patients ≥12 years of age in 2 identically designed double-blind, randomized, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2). In both studies, patients had 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 or vehicle BID 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 the difference 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 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 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]*.

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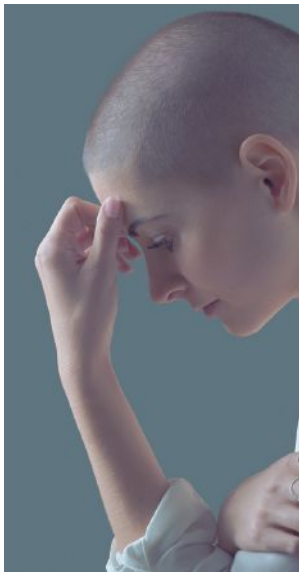

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***The Dermatology Digest* is Different**

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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IN THIS ISSUE

The month of January marks the beginning of a new year, with new opportunities for learning. True to our name, this first issue of 2022 features digestible content from several recent meetings, including the XIII International Congress of Dermatology (ICD 2021), 2021 ASDS Annual Meeting, 4th Inflammatory Skin Disease Summit, and 2022 Winter Clinical Dermatology Conference.

Inside, Dr. Jenny Murase advises on psoriasis treatment for women of childbearing age. Dr. Arisa Ortiz and Dr. Anthony Benedetto detail clinical (rather than cosmetic) uses for lasers and botulinum toxin, respectively. Others provide updates for vitiligo treatment, guidance for determining venous insufficiency, and considerations for the dermatologist on the organ transplant team.

A mainstay of each *TDD* issue, this month Dr. Ted Rosen, Medical-Editor-in-Chief, questions a recent attempt to vilify medical eponyms in "Ted Talks." (Tell us: do you agree?) Our cover story spotlights the growing subspecialty of oncodermatology and opportunities for dermatologists to help improve quality of life for cancer patients with skin sequelae. And we've got not one but two new FDA-approved drugs to detail (ruxolitinib for AD and ibrexafungerp for acute vulvovaginal candidiasis.) This month's Off-Label Pearl offers treatment for the elusive so-called "angry" red scrotum syndrome, and finally, in our Zebra, what's your diagnosis for this case of a gradually expanding and extremely painful penile lesion?

We hope that you find these topics to be as interesting as they are educational.

The Dermatology Digest

EDITORIAL BOARD

Ted Talks

Are Medical Eponyms Obsolete?

"What's in a name? That which we call a rose by any other name would smell just as sweet"

—William Shakespeare, *Romeo and Juliet*, Act 2, Scene 2

Ted Rosen, MD, FAAD
Editor-in-Chief

This is Ted's take.
What's yours?
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Maybe Australian gynecological anatomist Dr. Kristin Small and gynecologist Dr. Nisha Khot are on to something really important. They have recently issued a call to rename hundreds of body parts and multiple surgical procedures named after "old men, kings and gods." According to them, these eponyms are completely irrelevant and dangerously misogynistic. They teach their students to replace them with more practical, descriptive and neutral terminology. According to the *Daily Mail*, Dr. Small is simply tired of everything medical being named after "dead dudes." You can read about her passionate crusade at https://www.dailymail.co.uk/news/article-8537393/Sexist-body-terms-like-Adams-apple-no-longer-used-doctor-says.html.[1]

So what are we talking about? One prominent example these trailblazers cite is the term "Adam's apple" as a description of excessive laryngeal cartilage. Apparently, this phrase was first found in the 1662 English translation of the text *Anatomia* by Thomas Bartholin (1616-1680), a Danish physician. The term likely refers to a popular story that Adam, the first man according to Judeo-Christian theology, eventually expired when an apple (the "forbidden fruit") became lodged in his throat. The anatomical revisionists would prefer that this structure be called a "laryngeal prominence." In fact, they are a wee bit late, since the latter terminology already appeared

in a popular text of its day, the *Basle Nomina Anatomica* in 1895. Apparently, 126 years later, "laryngeal prominence" has not yet obliterated the highly objectionable "Adam's apple."

Another phrase which has drawn their ire is "Achilles tendon." Of course, this structure is the fibrous tendon which connects several calf muscles to the calcaneus (heel bone). Apparently, this phrase was first used by the Dutch anatomist and surgeon Philip Verheyen (1648-1710) in his 1693 textbook *Corporis Humani Anatomia*. The anatomist was almost certainly making reference to the mythological account of Achilles being held by the heel by his mother, Thetis, when she dipped him in the River Styx as a baby to render his body invulnerable. In so doing, she left his heel susceptible to injury. The

anatomical revisionists would have us drop Achilles tendon for either calcaneal tendon or heel cord.

Some other terms which might be endangered include: Eustachian tube (so named in honor of the sixteenth-century Italian anatomist Bartolomeo Eustachi), fallopian tubes (named in honor of the sixteenth-century Italian anatomist Gabriele Falloppio), and Bartholin glands (named after their first describer, seventeenth-century Danish anatomist Caspar Bartholin the Younger). Instead, we are urged to utilize these terms: pharyngotympanic tube, uterine tubes, and greater vestibular glands, respectively.

All this got me thinking about some terms we might eliminate in dermatology. The first to go has to be the dilated pore of Winer. Let's replace it with "really big nasal pore." Another one that irks me is Mucha-Habermann disease. It is also known only as Habermann disease. I lay awake at night wondering if Mucha should be there, or not? And we already have a perfectly pragmatic, easy-to-remember name: pityriasis lichenoides et varioliformis acuta. Hailey-Hailey disease needs to be totally replaced by chronic benign familial pemphigus--even though the juxtaposition of the words "benign" and "pemphigus" is slightly misleading. Why should we use the name Behcet's syndrome? Dr. Behcet published his research on this disorder in 1936, but the main components of the entity were actually first documented by Planner and Remenovsky in 1922 in the *Archiv für Dermatologie und Syphilis*. Rather than renaming this disease with a triple eponym, we should hold a national contest to come up with a new, concise, neutral appellation! Finally, although described in Wikipedia as "the father of modern academic dermatology" and "the most influential dermatologist of the last 100 years," we must vow to jettison the terminology Fitzpatrick Skin Type. Let's all agree to exclusively use the term "skin photophenotype." Believe me, there are many, many more suggestions I could make….As you can tell from my tone,

> **"I really don't think that medical eponyms are born from malevolent intent of any kind, let alone being racist or misogynist."**

I find the movement currently spearheaded by Small and Khot to be slightly narrow-minded and misguided. I really don't think that medical eponyms are born from malevolent intent of any kind, let alone being racist or misogynist. Mostly, naming an anatomical structure, a disease, or a specific procedure after prominent scientists who discovered or explained it or after famous patients who popularized it (e.g. Lou Gehrig's disease, Tommy John surgery) honors individuals. It helps tell a story of how this entity came to be, if one only takes the time to look it up. Many eponyms are so deeply ingrained in medicine and popular culture that their names provide a convenient shorthand for both physicians and patients. Case in point: use the term Hodgkin's Disease (with or without the apostrophe s), and the majority of medical providers and many laymen know precisely what it is.

When you consider historical precedent, widespread prevalence, and ease of use, I think eponyms are here to stay. Even if well-intentioned, to purge medicine of eponyms would be a massive, time-consuming and incredibly costly endeavor. Is this realistic? Is it even worth it? Truly humanitarian acts should supersede a kind of "cancel culture" witch hunt in medicine. In the time spent to be interviewed by the *Daily Mail* about the evils of eponyms, perhaps these Australian doctors might have better spent their efforts by providing pro bono care for one or more disadvantaged individuals. ◈

REFERENCE

Ferri L. New push to RENAME body parts like the Adam's apple and Achilles' tendon because they are 'irrelevant and misogynistic.' *DailyMail.com*. 2020 July 19. Accessed 2022 Jan 11.

Off-label Pearl

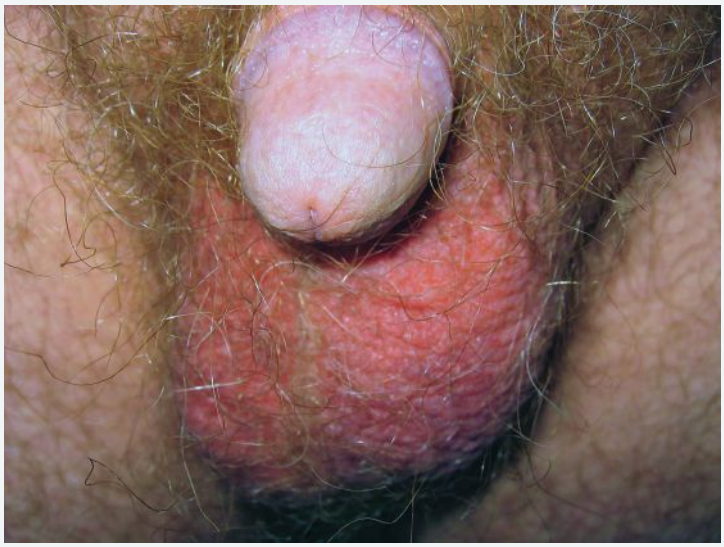
By Ted Rosen, MD, FAAD, Editor-in-Chief

Indomethacin for Burning Scrotum Syndrome

The cause of "angry red scrotum syndrome" (also known as the "burning scrotum syndrome") remains elusive. Other than a few cases which are due to erythema-only cutaneous candidiasis, which readily respond to topical or oral anti-*Candida* measures, there is no "surefire" way of treating this terribly distressing entity.

In the past, doxycycline (at standard dosages) has been recommended. In addition, both oral carvedilol and topical timolol maleate beta-blockade has been suggested to be effective, as have neuroleptic agents (such as gabapentin and pregabalin).

In my hands, none of these recommendations has been very successful. A recent publication suggested the use of indomethacin at a dose of 50 mg TID over an extended time period. I utilized this treatment on my three most recalcitrant patients with total symptomatic resolution after 3 to 6 months administration. It is theorized that the agent may be acting both as an anti-inflammatory and a vasoconstrictor. Remember that this potent NSAID can be associated with serious gastrointestinal bleeding, myocardial infarction and stroke, and should not be given to individuals who are allergic to aspirin and related agents.



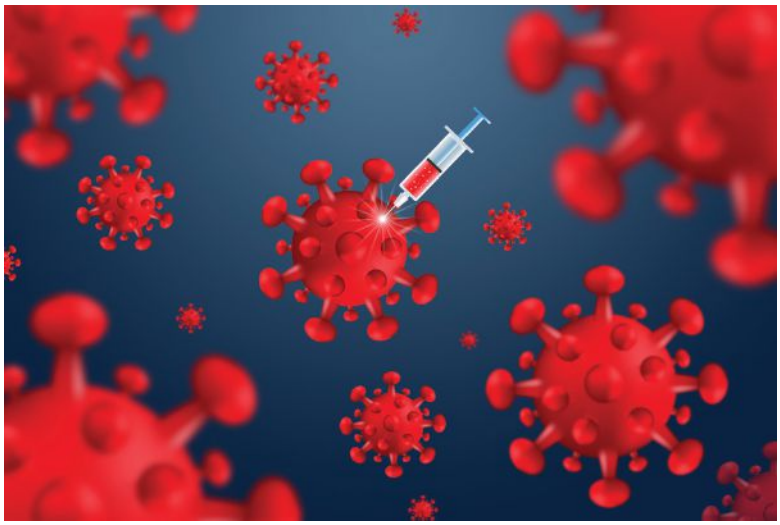
TO READ MORE: Hwang AS, Costello CM, Yang YW. Rapid improvement of burning scrotum syndrome with indomethacin. *JAAD Case Reports* 2021;7(12):32-33. doi: 10.1016/j.jdcr.2021.03.050.

Literature Lessons

COVID-19

A study compared individuals who received SARS-CoV-2 vaccination with and without prior COVID-19 infection. Individuals with prior COVID-19 infection followed by 2 doses of mRNA vaccine (3 separate exposures to spike antigen) developed higher spike **ANTIBODY** measurements than individuals who only received comparable vaccination.

TO READ MORE: Zhong D, et al. Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection. *JAMA*. 2021; November 1. doi:10.1001/jama.2021.19996.



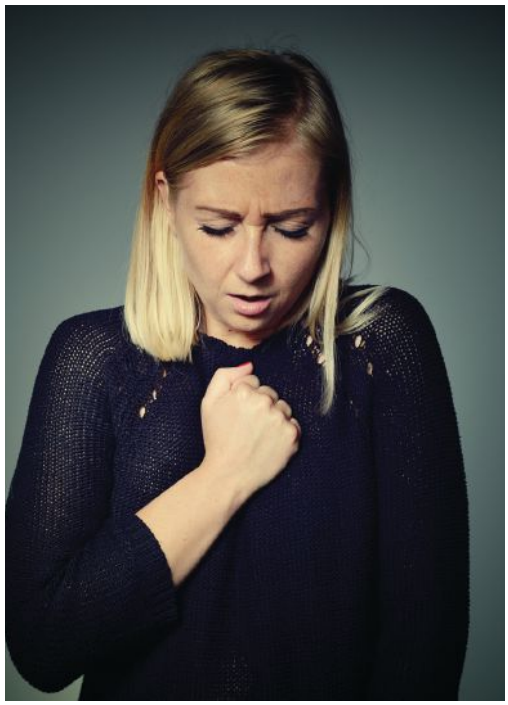
Prior SARS-CoV-2 vaccination reduces the overall death rate and severity of disease among those with **"BREAKTHROUGH"** infection compared to those who are hospitalized but did not receive vaccination.

TO READ MORE: Tenforde MW, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. *JAMA*. 2021; November 4. doi:10.1001/jama.2021.19499.

A single center (St. Joseph's Health Network, Paterson, NJ) prospective study found that 47.9% of verified COVID-19 patients had **PERSISTENT SYMPTOMS** a year after initial diagnosis. Most notably, patients experienced dyspnea, fatigue, anxiety, and difficulty focusing ("brain fog") regardless of whether they received solely outpatient care or required hospitalization.

TO READ MORE: Millet C, et al. "COVID-19: Other Considerations in Management." Presented at: the virtual CHEST Annual Meeting; 2021; Oct. 17-20.

(**Editor's note:** Similar publications have suggested both higher and slightly lower percentages of COVID-19 patients suffer from long term sequelae. It doesn't really matter what the "exact" number is, clinicians need to recognize that many people do experience important post-COVID problems for at least a year after their acute illness.)



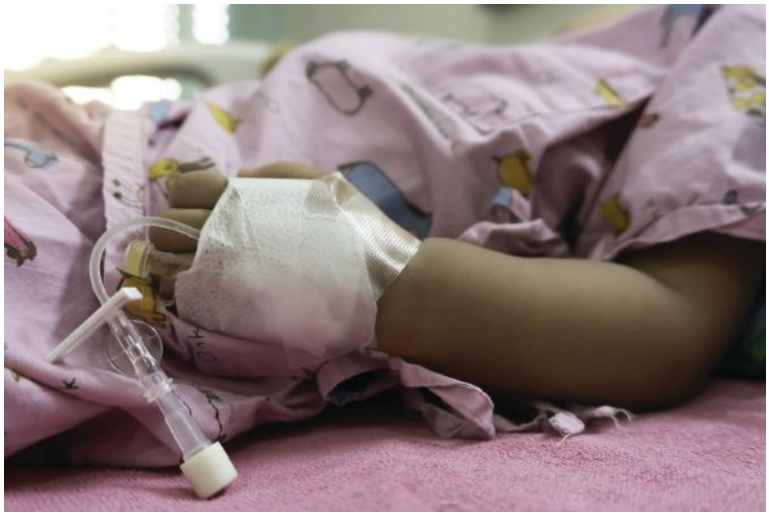
PEDIATRIC DERMATOLOGY

Patients with **KAWASAKI DISEASE** who do not have coronary aneurysms are not at increased risk for cardiac events in adulthood. In contrast, pediatric patients with persistent moderate to large aneurysms require ongoing cardiology care as adults (over age 18).

TO READ MORE: Dahdah N, et al. Falling Through the Cracks: The Current Gap in the Health Care Transition of Patients With Kawasaki Disease. *J Am Heart Assoc.* 2021; Oct. 19. doi: 10.1161/JAHA.121.023310.

A retrospective Chinese study included 1,398 patients with Kawasaki disease hospitalized in 7 affiliated facilities of Chongqing Medical University. Resistance to intravenous immunoglobulin (IVIG) and subsequent development of coronary aneurysms could be predicted (70% sensitivity, 90% specificity) by looking for four concurrent findings: elevated ALT, thrombocytopenia, elevated procalcitonin, and elevated total bilirubin.

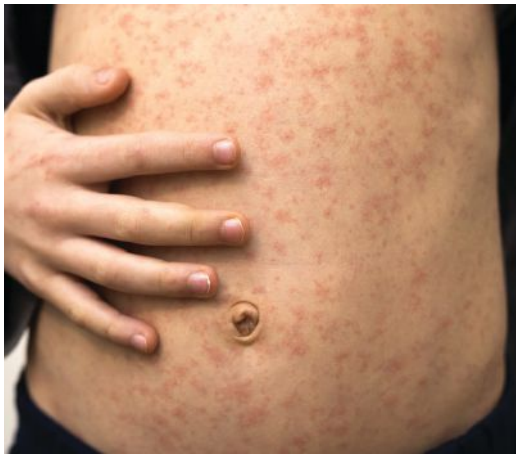
TO READ MORE: Liu J, et al. A Machine Learning Model to Predict **INTRAVENOUS IMMUNOGLOBULIN-RESISTANT KAWASAKI DISEASE** Patients: A Retrospective Study Based on the Chongqing Population. Front Pediatr. 2021; Nov 8. doi: 10.3389/fped.2021.756095.



DRUGS AND DEVICES

DRESS and maculopapular drug reaction patients were prospectively compared on a battery of clinical, biochemical and serological markers. With a sensitivity of 96% and a specificity of 100%, DRESS was diagnosed when the patient had body surface area involvement of >35% at baseline, and absolute eosinophil count of >450 cells/mm3, and a high-sensitivity C-reactive protein of >5mg /L.

TO READ MORE: Choudhary R, et al. Clinical, biochemical, and serologic predictors of drug reaction with eosinophilia and systemic symptoms syndrome: A prospective case-control study. *J Am Acad Dermatol.* 2021; Oct. doi: 10.1016/j.jaad.2021.03.075.



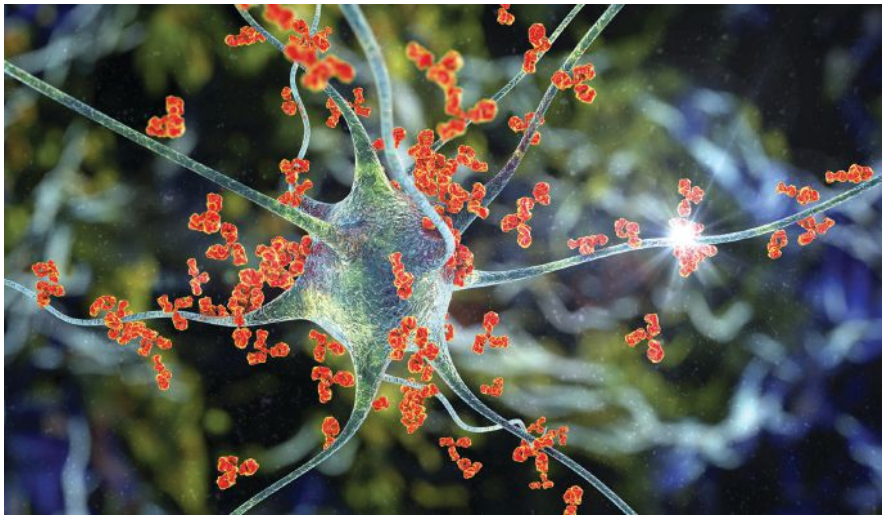
Extensive, prospective evaluation of 45 consecutive **DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)** patients at a single London hospital disclosed that extremely high fever, short latency, and persistent reaction were associated with more severe disease. The presence of facial edema also correlated with a severe disease course.

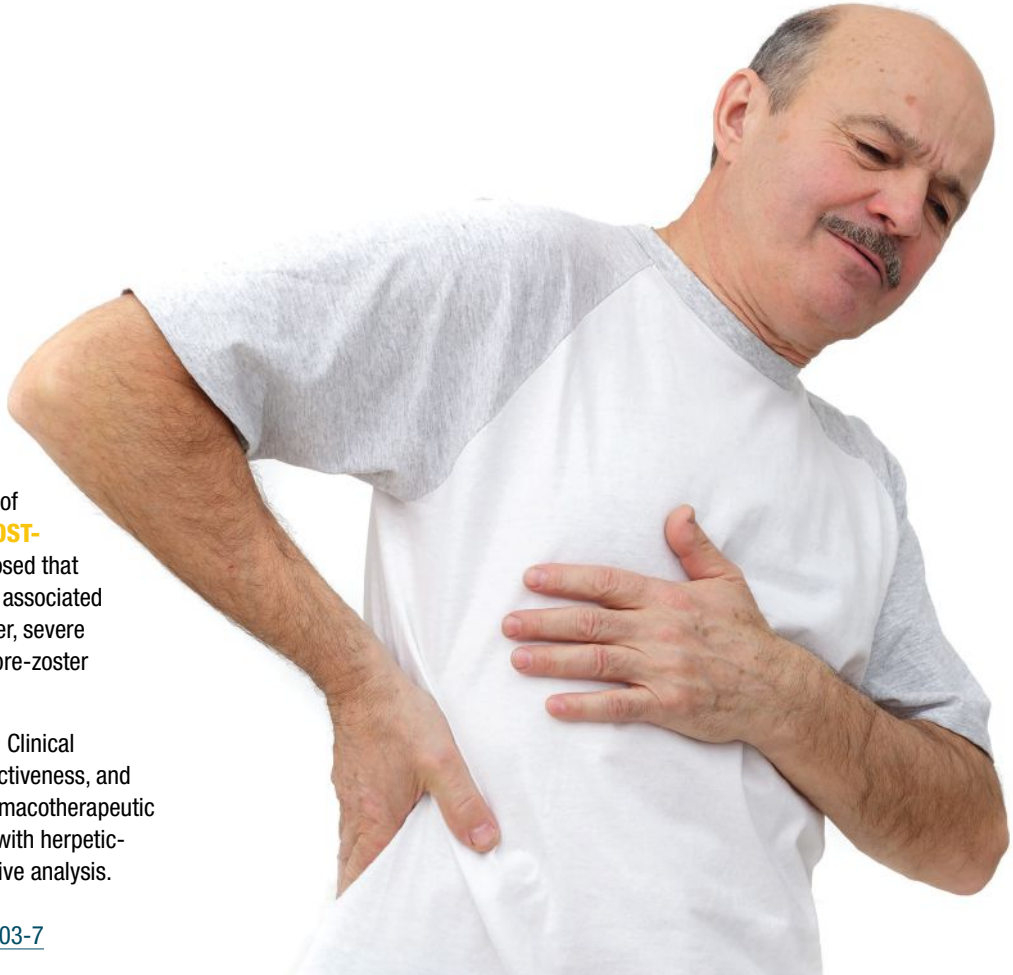
TO READ MORE: Momen SE, et al. Discriminating minor and major forms of drug reaction with eosinophilia and systemic symptoms: Facial edema aligns to the severe phenotype. *J Am Acad Dermatol.* 2021; Sept. doi: 10.1016/j.jaad.2021.04.020

(**Editor's note:** Sulfa drugs, carbamazepine, vancomycin, allopurinol, and phenytoin were common causes.)

A case series cohort study compared 849,397 Shingrix-vaccinated and 1,817,099 Zostavax-vaccinated Medicare beneficiaries aged 65 years or older. This study confirmed a prior analysis of the Vaccine Safety Datalink which showed an increased risk of Guillain-Barre Syndrome among those receiving Shingrix. However, the actual quantified risk is 3 excess cases of GBS per one million vaccinations administered.

TO READ MORE: Goud R, et al. Risk of Guillain-Barré Syndrome Following Recombinant Zoster Vaccine in Medicare Beneficiaries. *JAMA Intern Med.* 2021; Dec 1. doi:10.1001/jamainternmed.2021.6227.





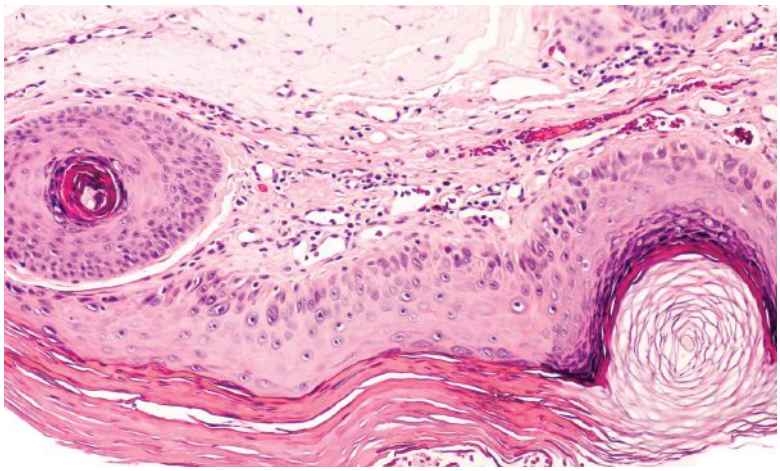
A retrospective Chinese study of 213 patients suffering from **POST-HERPETIC NEURALGIA** disclosed that medication resistant pain was associated with older age and male gender, severe lesions at disease onset, and pre-zoster anxiety or depression.

TO READ MORE: Zhou J, et al. Clinical characteristics, treatment effectiveness, and predictors of response to pharmacotherapeutic interventions among patients with herpetic-related neuralgia: A retrospective analysis. *Pain Ther.* 2021; Dec. doi:10.1007/s40122-021-00303-7

CUTANEOUS ONCOLOGY, SURGERY AND LASERS

This study, the largest **ACTINIC KERATOSIS** genomic dataset to date, demonstrates that actinic keratosis and cutaneous squamous cell carcinomas are remarkably similar at the genomic level in terms of tumor mutational burden, patterns of driver genes, and copy number aberration. Dysregulated TGFβ signaling may represent an important event in AK to cSCC progression.

TO READ MORE: Thomson J, et al. The Genomic Landscape of Actinic Keratosis. *J Invest Dermatol.* 2021; July. doi:10.1016/j.jid.2020.12.024.



Prior studies had indicated an alarming increase in the proportion of dermatological surgery patients who received a post-op narcotic analgesic. However, this recent cross-sectional, nationally representative study using Optum Clinformatics DataMart shows that the proportion of Mohs surgery patients receiving a prescription for an **OPIOID** agent has been declining in recent years. The authors speculate that this represents response of both dermatologic surgeons and patients to public health concerns regarding the opioid epidemic.

TO READ MORE: Veerabagu SA, et al. Rates of opioid prescriptions obtained after Mohs surgery. A claims database analysis from 2009 to 2020. *JAMA Dermatol.* 2021; Nov 1. doi: 10.1001/jamadermatol.2021.3468.

A retrospective Portuguese study strongly suggests that pretreatment of head and neck non-superficial basal cell carcinomas with **IMIQUIMOD** resulted in a significantly reduced number of Mohs micrographic surgery stages until clearing and fewer complex closures required. Imiquimod was administered five times weekly for six weeks in advance of the definitive procedure.

TO READ MORE: Queirós C, et al. Topical imiquimod as neoadjuvant therapy before Mohs micrographic surgery for basal cell carcinoma in the head and neck region: findings from a large retrospective study. *Br J Dermatol.* 2021; Oct. doi: 10.1111/bjd.20487.

HAIR AND NAILS

A roundtable discussion among well-known experts in **ONYCHOMYCOSIS** recommended combining both topical and oral therapy for elderly, diabetic and immunocompromised patients, as well as those who have more extensive disease.

TO READ MORE: Lipner SR, et al. Therapeutic Recommendations for the Treatment of Toenail Onychomycosis in the US. *J Drugs Dermatol.* 2021; Oct 1. doi: 10.36849/JDD.6291.

ALOPECIA is among the most distressing events associated with chemotherapy. Scalp cooling can prevent or, at least, minimize the adverse event. However, there is a significant geographic disparity related to the availability (and therefore use) of scalp cooling. Nearly a third of all Medicare-billed chemotherapy infusions occur 50 or more miles away from a center offering scalp cooling. Suburban and rural areas seemingly have the fewest centers immediately available for scalp cooling.

TO READ MORE: Singer S, et al. Geographic disparities in access to scalp cooling for the prevention of chemotherapy-induced alopecia in the United States. *J Am Acad Dermatol.* 2021; Nov. doi: 10.1016/j.jaad.2020.06.073.

A small, prospective Phase 2 study of Black breast cancer patients receiving scalp cooling as a preventative intervention for **CHEMOTHERAPY-INDUCED ALOPECIA** was discontinued early due to a clear lack of efficacy. Grade 3 alopecia (>50% hair loss) was observed in 93% of Black study participants.

TO READ MORE: Dilawari A, et al. Does Scalp Cooling Have the Same Efficacy in Black Patients Receiving Chemotherapy for Breast Cancer? *Oncologist.* 2021 Apr. doi: 10.1002/onco.13690.

(**Editor's note:** Initial large-scale studies on this modality were done in Europe with nearly all subjects being Caucasian.)

A retrospective review of 842 medical records matched for gender, age, and ethnicity were reviewed to detect differences between dermatologic disorders among homeless and non-homeless individuals. The most striking difference was an increase in infectious diseases (bacterial, fungal and ectoparasitic) among the homeless.

TO READ MORE: O'Quinn M, et al. Cutaneous Manifestations and Clinical Disparities in Patients Without Housing. *Cutis*. 2021; Oct. doi: 10.12788/cutis.0367.

A method of laser-related, painless, **NEEDLE-FREE INJECTION** has been developed by Dutch scientists. Within a millisecond, laser-formed heat pushes the injectable liquid into the skin at a speed of over 60 miles per hour, with virtually no pain. Full-scale clinical trials will begin shortly.

TO READ MORE: Verkaik E. 'Virtually painless' needle-free injections developed in the Netherlands. Reuters. 2021; Oct 13. 'Virtually painless' needle-free injections developed in Netherlands | Reuters. Accessed Jan 17, 2022.

AUTOECZEMATIZATION, or "id reaction," is most commonly seen in association with tinea pedis and severe stasis dermatitis. In children, tinea capitis can cause autoeczematization. Id reaction presents as an intensely pruritic eruption of vesicles which may crust and turn into papules. The most important thing is to treat the underlying disorder.

TO READ MORE: Bertoli MJ, et al. Autoeczematization: A strange id reaction of the skin. *Cutis*. 2021; Sept. doi: 10.12788/cutis.0342.

An online Chinese survey disclosed that 204 or 409 **VITILIGO** patients suffered from insomnia. Many indicated that the initial appearance, worsening or recurrence of vitiligo, particularly involving the head and neck, were associated with the onset of insomnia. Female vitiligo patients were about twice as likely as male patients to develop insomnia.

TO READ MORE: Liu JW, et al. Location, Spreading and Oral Corticosteroids are Associated with Insomnia in Vitiligo Patients: A Case–Control Study. *Clin Cosmet Investig Dermatol*. 2021; August 3. doi: 10.2147/CCID.S322963.

A retrospective analysis from Taiwan using that country's National Health Insurance Research Database compared 23,509 individuals with **HEPATITIS C** virus infection to 94,036 age and sex-matched controls without HCV infection. Those with HCV infection were more likely than controls to develop psoriasis, lichen planus, vitiligo, alopecia areata and cutaneous lupus erythematosus. The median duration between HCV infection and the onset of inflammatory skin disease was 3.4 years.

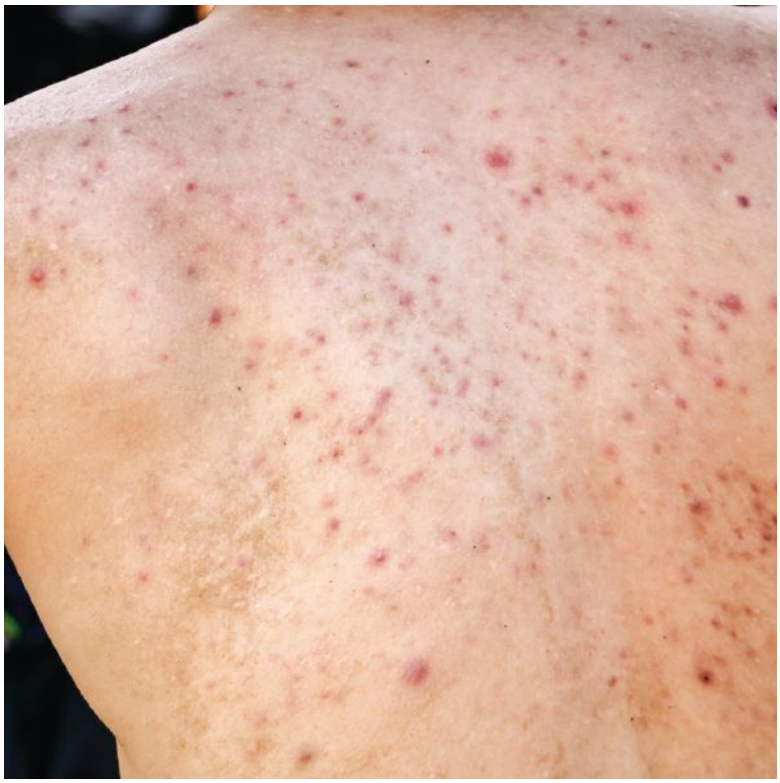
TO READ MORE: Ma SH, et al. Association between hepatitis C virus infection and subsequent chronic inflammatory skin disease. *J Dermatol*. 2021; Dec. doi: 10.1111/1346-8138.16129.

ACNE

Utilizing the IBM MarketScan Research Databases, investigators found that acne patients treated with **ISOTRETINOIN** did not show an increase in suicidal ideation or suicide attempt compared to either acne patients treated with antibiotics or the general age-matched population.

TO READ MORE: Ugonabo N, et al. Psychiatric disorders and suicidal behavior in patients with acne prescribed oral antibiotics versus isotretinoin: Analysis of a large commercial insurance claims database. *J Am Acad Dermatol.* 2021; Oct. doi: 10.1016/j.jaad.2021.01.107.

(**Editor's note:** Although all recent literature speaks against isotretinoin administration as a cause of suicidal ideation or suicide attempts, I still like to have written clearance from the mental health professional who might be providing counseling to my isotretinoin patients.)



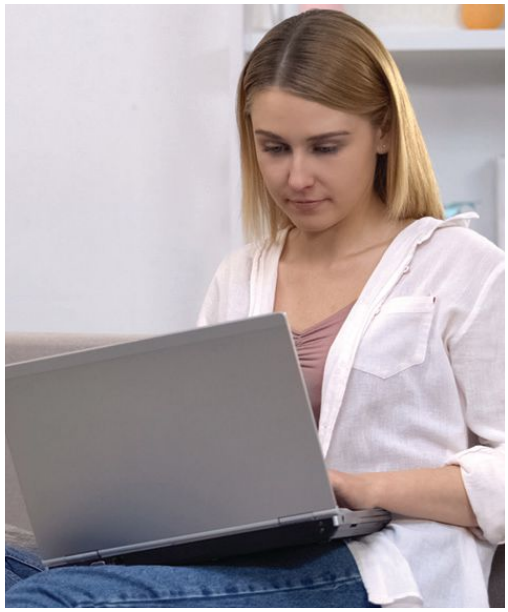
SARECYCLINE, a narrow spectrum tetracycline derivative already approved for moderate to severe acne, was specifically evaluated for chest and back acne. It was found to be effective for these more difficult areas.

TO READ MORE: Del Rosso JQ, et al. Management of Truncal Acne With Oral Sarecycline: Pooled Results from Two Phase-3 Clinical Trials. *J Drugs Dermatol.* 2021; June. doi: 10.36849/JDD.2021.6204.

ATOPIC DERMATITIS

Patients who seek information on atopic dermatitis often turn to **INTERNET VIDEOS**. Patients favor lay produced rather than professional produced products, despite the fact that the latter are more reliable and of higher quality.

TO READ MORE: Martin A, et al. Atopic dermatitis topical therapies: Study of YouTube videos as a source of patient information. *Cutis* 2021; Sept. doi: 10.12788/cutis.0333.



A 24-week head-to-head, multi-national, randomized, double-blinded study compared oral **UPADACITINIB** (30mg daily) to subcutaneous dupilumab (300mg every other week) in adult patients with atopic dermatitis. About 340 subjects received each agent. A higher percentage of those who received upadacitinib achieved EASI75 and EASI100. However, upadacitinib was associated with an increased risk of serious infection (eczema herpeticum and herpes zoster) and laboratory-related adverse events.

TO READ MORE: Blauvelt A, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis. A randomized Clinical Trial. *JAMA Dermatol.* 2021; Sept. doi:10.1001/jamadermatol.2021.3023. ◈

Expanding the AD Treatment Armamentarium

With Lawrence F. Eichenfield, MD

New topical nonsteroidal improves signs and symptoms of AD

LAWRENCE F. EICHENFIELD, MD

Professor of Dermatology and Pediatrics, University of California, San Diego

The FDA approval of ruxolitinib 1.5% cream (Opzelura, Incyte) for the treatment of atopic dermatitis (AD) provides dermatologists with a new nonsteroidal option offering both anti-inflammatory and anti-pruritic activity.

"Ruxolitinib is the first janus kinase (JAK) inhibitor approved for treating AD and the first approved topical JAK inhibitor. Ruxolitinib blocks JAK1 and JAK2 and provides dual benefits for treating AD because the JAK-Stat pathway mediates inflammation and may also mediate itch," said Lawrence F. Eichenfield, MD, Professor of Dermatology and Pediatrics, University of California, San Diego.

"In two 8-week phase 3 studies, over 50% of patients using ruxolitinib 1.5% cream twice daily achieved treatment success defined as an Investigator's Global Assessment rating of 'clear or almost clear' with at least a 2-step improvement from baseline. Mean itch score for the entire cohort averaged around 5 at baseline on a scale of 0 to 10, and among patients with an itch score of at least 4 at baseline, more than 50% had at least a 4-point decrease at week 8. Significant itch reduction versus vehicle control was even seen within 12 hours after the first use."

Treatment with topical ruxolitinib was also safe and well-tolerated in the pivotal trials.

"Rates of application site burning and pruritus, which were the most common treatment-related adverse events, were very low (<1%) in the ruxolitinib 1.5% cream group and lower than in the control group," Dr. Eichenfield said.

"The prescribing information contains Black Box warnings about adverse events, but they mostly reflect experience with oral JAK inhibitors. Pharmacokinetics data show no evidence of systemic accumulation with topical ruxolitinib application over time."

Dr. Eichenfield added that ruxolitinib cream is indicated for short-term and non-continuous chronic treatment for patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, and it is recommended to be applied to no more than 20% of the body surface area.

TABLE. Topical Ruxolitinib for AD: pivotal trial outcomes

Endpoint	**Ruxolitinib 1.5% cream** (n = 481)	**Vehicle** (n = 244)
% of patients achieving		
IGA success (score of 0-1 and 2-grade improvement)	51.1% to 53.8%	7.6% to 15.1%
EASI-90 score	43.4% to 44.3%	4.2% to 9.5%
Clinically meaningful itch reduction (≥4-point improvement)	50.7% to 52.2%	15.4% to 9.5%

IGA, Investigator's Global Assessment; EASI-90, ≥90% improvement in Eczema Area and Severity Index at week 8 versus baseline

The prescribing information contains Black Box warnings about adverse events, but they mostly reflect experience with oral JAK inhibitors. Pharmacokinetics data show no evidence of systemic accumulation with topical ruxolitinib application over time.

"The average body surface area of involvement for patients in the phase 3 pivotal trials was just under 10%, and the treatment was used for 8 weeks," he said.

"Data from patients participating in an extension of the phase 3 trials offer evidence that could support the safety and efficacy of longer-term use. In the 1-year extension study, patients used ruxolitinib when their AD was not clear or almost clear, and stopped it when it was. The extent of treatment in this 'real-life protocol' was variable over the year, but no new safety signals emerged."

Role in the AD treatment algorithm

Although topical ruxolitinib was studied as monotherapy in the phase 3 trial, Dr. Eichenfield expects that dermatologists will likely also be using it in combination with other topical agents or even systemic treatments for AD. He suggested it could be considered as the initial topical treatment, but expects it is unlikely that dermatologists will routinely choose topical ruxolitinib instead of a topical corticosteroid.

"It is not very practical to abandon traditional therapeutic approaches, and topical triamcinolone and other steroids are used widely and successfully in regimens of AD patient care. Of course, topical steroids must be used properly and have limitations," Dr. Eichenfield said.

"As a topical nonsteroidal medication, however, ruxolitinib should prove very helpful when used early in the AD treatment regimen for 'delicate areas' that are at higher risk of steroid atrophy or to complement or replace other topical treatments."

Topical ruxolitinib has not been directly compared against other nonsteroidal treatments for AD. In a phase 2 randomized trial, outcomes were a little better among patients treated with ruxolitinib cream than controls using 0.1% triamcinolone cream.

"Triamcinolone, a mid-strength topical steroid, is a workhorse for treating AD. The results of the phase 2 trial suggest that ruxolitinib may be more efficacious than topical calcineurin inhibitors or crisaborole (Eucrisa, Pfizer)," Dr. Eichenfield said.

Results from the phase 3 AD studies are published.[1]

By Cheryl Guttman Krader

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1. 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.* 2021;85(4):863-872. doi:10.1016/j.jaad.2021.04.085.

DISCLOSURE

Dr. Eichenfield was an investigator in the ruxolitinib cream clinical trials and has served as a consultant or investigator for Abbvie, Almirall, Aslan, Dermavant, Lilly, Forte, Galderma, Incyte, Leo, Novartis, Ortho Dermatologics, Otsuka, Pfizer and Sanofi-Regeneron.

THE Dermatology Digest PRESENTS

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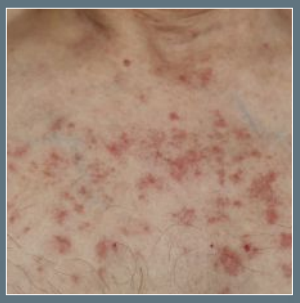
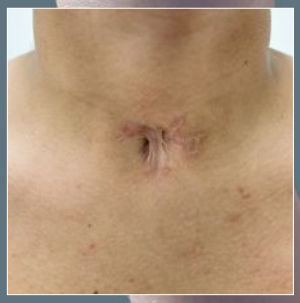
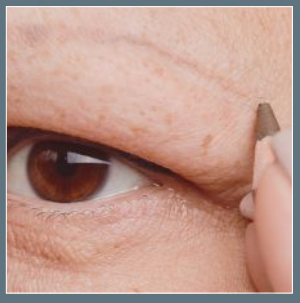
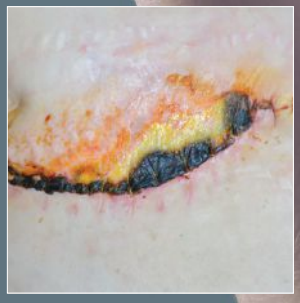
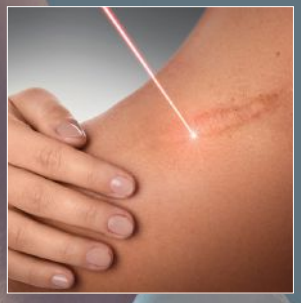






Dr. Anthony Rossi discusses and provides pearls for recognizing and caring for cancer patients' dermatologic sequelae to improve quality of life.

"Even though today's cancer therapies are highly effective at treating cancer, many patients are left with dermatologic sequelae from therapy that can impact them physically, psychosocially, and remind them of the cancer," said Anthony M. Rossi, MD, Mohs surgeon and Assistant Attending at Memorial Sloan Kettering Cancer Center, New York, New York.

"You do not have to work at a cancer center to take an interest in onco-dermatology, a subset of dermatology focused on treating patients that have active cancers and are going through therapy or patients that were treated for cancer and are now living with the sequelae."

According to Dr. Rossi, cancer treatment commonly and greatly affects how patients feel about their skin, hair, nails, and overall quality of life.

Cancer patients' long-term survival has doubled in recent decades, and it is projected that U.S. cancer survivors will approach 22.1 million by 2030. Along with treatment success comes an increase in dermatologic side effects. Nearly 60% of adult survivors of childhood cancer reported dermatologic issues. And up to one-third of all cancer patients point to dermatologic sequelae as the most impactful cancer therapy consequence, according to a review by Dr. Rossi and coauthors in the *Journal of the American Academy of Dermatology*.[1][Restorative oncodermatology: Diagnosis and management of dermatologic sequelae from cancer therapies - *Journal of the American Academy of Dermatology* (jaad.org)]

Specific Skin Issues

The review addresses how dermatologists might safely and effectively treat cancer therapy sequelae.

"Traditional chemotherapy can result in a host of skin issues, from rashes to hair loss, skin cracking, and fissuring. With the advent of more targeted therapies, like small molecule inhibitors and even more so with immunotherapies that are revving up our immune system to fight cancer, we are seeing different skin issues. For example, immunotherapy can cause a rash or induce a vitiligo-like type of depigmentation," said Dr. Rossi.

Therapies can affect skin in a way that may not initially be visible but can affect dermatologic treatment outcomes. For example, targeted therapies, such as the vascular endothelial growth factor inhibitor bevacizumab, severely impair wound healing, said Dr. Rossi.

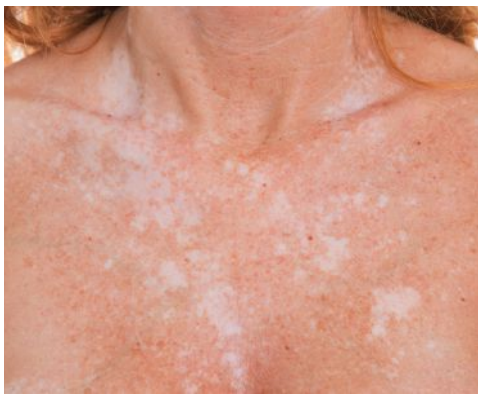
"Radiation therapy for breast cancer can result in chronic radiation dermatitis, leaving telangiectasias on the radiated skin that continue to grow many years after radiation is completed."

As a result, his patients describe feeling limited in their clothing options and even embarrassed to expose their skin to partners, said Dr. Rossi.

"I did a pilot trial using the pulsed dye laser to treat breast telangiectasias in women who had breast cancer and not

ANTHONY M. ROSSI, MD, FAAD, FACMS
Assistant Attending, Memorial Sloan Kettering Cancer Center
Assistant Professor, Weill Cornell Medical College
Assistant Attending, New York Presbyterian Hospital

"Radiation therapy for breast cancer can result in chronic radiation dermatitis, leaving telangiectasias on the radiated skin that continue to grow many years after radiation is completed."



"Dermatologists have an important part to play in the care of cancer patients—not only in the treatment of their skin, hair and nails during cancer therapy, but also in letting patients know that dermatologic manifestations after cancer therapy can safely be treated."

only was the laser successful at treating the telangiectasias, but we showed how you can do it with safe parameters to avoid injuring the skin. That is important because radiated skin is more fragile than nonradiated skin."[2] [Radiation-induced Breast Telangiectasias Treated with the Pulsed Dye Laser (nih.gov)]

Dr. Rossi authored the paper "Effect of Laser Therapy on Quality of Life in Patients With Radiation-Induced Breast Telangiectasias," [Effect of Laser Therapy on Quality of Life in Patients With Radiation-Induced Breast Telangiectasias (nih.gov)] and found the treatment dramatically improves not only the physical but also the social and psychosocial domains.[3]

"Radiation can harden the skin, a condition called radiation fibrosis. To treat it, we use the fractional CO2 laser, which drills microscopic holes in the skin to improve skin collagen growth and skin flexibility and viability."

Scars

Scarring from surgical procedures to treat cancer is also common. Even tracheostomies can leave very visible scars that can be improved with scar revision surgery or with lasers.

"Lasers are my go-to for scars, but when treating cancer patients who have been treated surgically and radiated, we have to take this slowly and conservatively because the skin may not heal as well. We take time to explain to the patient that this is more of a long-term gain."

Hair Loss

Chemotherapy can result in permanent chemotherapy-induced alopecia, and endocrine therapy can cause endocrine-induced alopecia.

"I have an ongoing clinical trial using platelet-rich plasma (PRP) for these types of hair loss. We are hoping to finish in 2022 and publish our results," said Dr. Rossi.

(Anti)Aging

"I am very much interested in the aging that happens when people undergo cancer therapy. This is an evolving area but… we can use lasers, neurotoxins, and injectable fillers in a safe, effective manner. We report in the article when you should time these."

The key, said Dr. Rossi, is to provide oncodermatology in concert with the patient's oncology team.

"[An] example of why it is important to talk with a patient's surgeon or oncologist is if you are lasering the chest of women who have been radiated who may have breast implants. You have to be careful in terms of how the breast reconstruction was done. If the implant is above the muscle, that skin that creates the breast flap is thin and if it is radiated, it is even thinner and can break down causing implant loss."

Dermatologists have an important part to play in the care of cancer patients—not only in the treatment of their skin, hair and nails during cancer therapy, but also in letting patients know that dermatologic manifestations after cancer therapy can safely be treated.

"A lot of oncologists may not know these treatments are available, so we are trying to spread the word not only in dermatology but also all the other specialties." ◈

By Lisette Hilton

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THE Dermatology Digest PRESENTS

Treating Non-Melanoma Skin Cancer

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November 2021 – January 2022

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Introductory Video

TheDermDigest.com/Non-MelanomaSkinCancer

Presented by:

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Director

Center for Cosmetic Enhancement,
Center for Clinical and Cosmetic Research, Aventura, Florida

Voluntary Professor

Department of Dermatology and Cutaneous Surgery
Department of Surgery, Division of Plastic Surgery
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November 2021	Part 1: Core Concepts and Treatment Modalitites in Non-Melanoma Skin Cancer
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Novel Oral Antifungal Treatment for Vulvovaginal Candidiasis

With Jack D. Sobel, MD

JACK D. SOBEL, MD

Professor of Medicine (Infectious Diseases) and Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan

Dr. Jack Sobel talks about ibrexafungerp, a first-in-class oral triterpenoid antifungal agent approved for the treatment of acute vulvovaginal candidiasis.

"Ibrexafungerp (Brexafemme, Scynexis) is a first-in-class oral triterpenoid antifungal agent approved for the treatment of acute vulvovaginal candidiasis (VVC). Post approval clinical experience is needed to fully understand the optimal use of ibrexafungerp as it is with any novel drug. Nonetheless, the availability of ibrexafungerp is an exciting development for expanding the therapeutic options for patients with VVC," said Jack D. Sobel, MD.

Dr. Sobel, Professor of Medicine (Infectious Diseases) and Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, was an investigator in pre-marketing clinical studies that supported FDA approval of ibrexafungerp for treating acute VVC. Although women with symptoms of VVC most often seek care from their gynecologist or primary care physicians, information about ibrexafungerp is of interest to dermatologists who may be called on to treat VVC because of its association with antibiotics used to treat acne, rosacea, and other dermatologic diseases.

"Single dose oral fluconazole is a widely used option for treating VVC, and a good choice considering its overall efficacy, safety, and

availability in generic form. Nevertheless, fluconazole suffers from a variety of limitations, including its potential for cytochrome P450 (CYP)-mediated drug interactions and for causing adverse events that include alopecia and idiosyncratic hepatotoxicity. Moreover,

TABLE. Outcomes in phase 3 pivotal trials of ibrexafungerp for treatment of VVC

Endpoint	VANISH 303			VANISH 306		
	Ibrexafungerp (n = 188)	Placebo (n = 98)	*P*	Ibrexafungerp (n = 188)	Placebo (n = 84)	*P*
Clinical cure	50.5%	28.6%	<.001	63.3%	44.0%	.0007
Mycological eradication	49.5%	19.4%	<.001	58.5%	29.8%	<.001
Overall therapeutic success	36.0%	12.6%	<.001	46.1%	28.4%	.022
Sustained symptom resolution	59.6%	44.9%	.009	73.9%	52.4%	.001

Candida resistance to fluconazole is a growing concern," said Dr Sobel.

"Ibrexafungerp has a different mechanism of action compared to the azole antifungals. It is a glucan synthase enzyme inhibitor that blocks the production of (1,3)-β-D-glucan polymers that are integral for fungal cell wall strength, and it has broad-spectrum anti-*Candida* fungicidal activity, including against *C. albicans* and other *Candida* isolates showing echinocandin and azole resistance. Ibrexafungerp was well-tolerated in clinical trials without evidence of causing renal, hepatic, or systemic safety issues, and drug interaction studies indicate that ibrexafungerp has a low potential for any cytochrome P450-mediated drug interactions."

Phase 3 study data

The pivotal trial program investigating ibrexafungerp involved two identically designed studies – VANISH 303, which was conducted entirely in the United States, and VANISH 306, which had sites in the United States and Bulgaria.[1,2]

Both studies randomized participants 2:1 to a 1-day course of ibrexafungerp 300 mg (2x 150 mg) BID or placebo BID. Both studies met their primary end point that assessed the percentage of patients achieving clinical cure, which was stringently defined according to current FDA criteria as complete resolution of VVC signs and symptoms (Table). Ibrexafungerp also demonstrated statistical superiority to placebo in secondary end points

Although women with symptoms of VVC most often seek care from their gynecologist or primary care physicians, information about ibrexafungerp is of interest to dermatologists who may be called on to treat VVC because of its association with antibiotics used to treat acne, rosacea, and other dermatologic diseases.

Available data indicate that compared with oral fluconazole, ibrexafungerp is at least as effective as a single dose of fluconazole for treating uncomplicated symptomatic VVC and may offer better efficacy based on analyses of sustained response rates.

analyzing mycological eradication and overall success rates (absence of signs and symptoms plus vaginal swab culture negative for *Candida* species growth) (Table).

Post-hoc analyses in VANISH 303 showed outcomes with ibrexafungerp were similar in Black women and those with higher body mass index (>35 kg/m2) compared with the overall population.

Ibrexafungerp was generally well-tolerated and had a favorable safety profile across the premarketing clinical trial program, including in phase 1 studies where subjects received single oral doses of up to 1600 mg and multiple oral doses of up to 800 for 28 days. The most common treatment-emergent adverse events associated with ibrexafungerp in the phase 3 studies and occurring at rates higher than in the placebo group were gastrointestinal in nature and included diarrhea/loose stool (16.7%), nausea (11.9%), and abdominal pain (11.4%). These adverse events were generally mild to moderate in severity and did not lead to treatment discontinuation.

Clinical perspectives

Available data indicate that compared with oral fluconazole, ibrexafungerp is at least as effective as a single dose of fluconazole for treating uncomplicated symptomatic VVC and may offer better efficacy based on analyses of sustained response rates. While medication cost/insurance coverage is usually the deciding factor in treatment selection, certain patient characteristics might favor ibrexafungerp as the antifungal drug of choice for certain women with VVC, according to Dr Sobel.

He said, "Ibrexafungerp should be considered for women with fluconazole allergies or a history of intolerance, and it is likely preferred for patients with refractory symptomatic disease as they may be expected to have infection with a fluconazole-resistant species."

Dr. Sobel noted that like fluconazole, ibrexafungerp is contraindicated for use in pregnancy due to the risk of fetal harm.

"Therefore, we still await an alternative oral treatment for VVC that fills the gap for use during pregnancy," he said.

He also observed that women enrolled in the ibrexafungerp clinical trials predominantly had mild to moderately severe uncomplicated VVC caused by *C. albicans*.

"A phase 3 study is investigating ibrexafungerp for the treatment of recurrent VVC. Research is also needed to determine its efficacy for treating severe forms of VVC and cases caused by non-*albicans Candida* sp. or azole-resistant *Candida*. Fortunately, the latter affect only a minority of women with VVC. ◈

By Cheryl Guttman Krader

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DISCLOSURES

Dr. Sobel is a consultant to Scynexis.

THE Dermatology Digest PRESENTS

Newly Approved Treatments for Parasitic Skin Infections

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JANUARY – FEBRUARY 2022

Featuring: Dr. Ted Rosen, MD and Dr. Christopher Belcher, MD

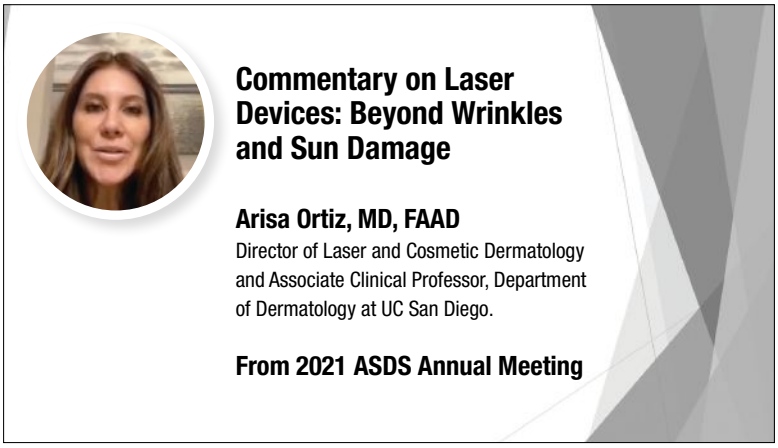
VIDEOS

- Newly Approved Treatments for Parasitic Skin Infections
- Current Scabies Treatment Paradigms
- Case-Based Management of Scabies

Medical Use of Laser Devices

With Arisa Ortiz, MD, FAAD

Dr. Arisa Ortiz discusses laser treatment with the 1064 nm Nd:YAG for medical indications that affect the skin.



WATCH: https://thedermdigest.com/uncategorized/medical-use-of-laser-devices

"There are so many medical indications that we use [lasers] for and so my focus was the 1064 nm Nd:YAG laser," said Arisa Ortiz, MD, FAAD, a presenter in the session "Already Have a Laser Device? Think Beyond Wrinkles and Sun Damage" at the 2021 American Society for Dermatologic Surgery (ASDS) Annual Meeting. Each presenter in the session focused on a specific modality.

Port Wine Stains

"One of the things that I use it for is thicker port wine stains—port wine stain birthmarks."

Superficial wavelengths are not effective for treating port wine stains that have vascular blebs or have developed deeper vessels over time, said Dr. Ortiz.

"I commonly will use a combination of the 1064 nm Nd:YAG laser to get the deeper component, like the blebs or the thicker port wine stain portions, and then I'll combine that with more superficial wavelengths like the pulsed dye laser or KTP laser.

Because the 1064 nm Nd:YAG laser absorbs oxyhemoglobin, this laser isn't for the inexperienced dermatologist, cautioned Dr. Ortiz.

"…there might be arterial absorption. It's not a beginner laser in that sense because it may cause ulceration and so you have to be very careful. I space the pulses far apart so that there's no ulceration or scarring."

BCC

As a Mohs surgeon, Dr. Ortiz said she focuses much of her research on finding safe and efficacious noninvasive treatments for skin cancer. She published a recent study showing a 90% histologic clearance rate of basal cell carcinoma (BCC) after a single treatment with the 1064 nm Nd:YAG laser.[1]

"I focus mostly on non-Mohs criteria tumors, so off of the face, non-aggressive subtypes, but it's just a single treatment. It's coded under a destruction code, so it's covered by insurance. It's just for patients that are poor surgical candidates or those that are surgically exhausted. It's a nice alternative for them—another modality that we have in our armamentarium."

However, Dr. Ortiz said she does sometimes make exceptions for treating tumors on the face in older patients with multiple tumors.

In another (unpublished) study, Dr. Ortiz found only 1 of 34 tumors recurred after a single treatment with the 1064 nm Nd:YAG laser.

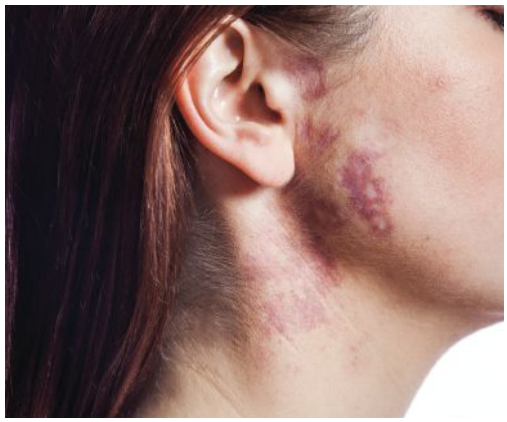
"I think that we have a lot of good data now showing that it's a good alternative and clearances are even better than [with] some of the topicals that we use."[2]

Acne

The 1064 nm Nd:YAG also has a role for acne patients interested in or need alternative treatments, whether they are concerned about their microbiome health, antibiotic averse, or not responding to traditional treatments, said Dr. Ortiz.

"I still think medical therapy is the first line but for those patients who either aren't responding or don't want to take antibiotics, then I really like using the of 1064 nm Nd:YAG specifically with the 650 microsecond pulse."

According to Dr. Ortiz, the 1064 nm Nd:YAG acne treatment protocol is for a total of 4 treatments, every 1 to 2 weeks. Patients experience no pain or downtime, she said.



"It's a great alternative treatment for acne."

Pseudofolliculitis Barbae

Because the 1064 nm Nd:YAG has a longer wavelength, it bypasses epidermal melanin making it safe for all skin types, including types 5 and 6, said Dr. Ortiz.

"There's a condition called pseudofolliculitis barbae where [darker skin types] get inflammation of the follicles, and you can treat that with hair removal."

Medical vs. Cosmetic

Despite growing evidence that supports the medical use of laser devices, such as the 1064 nm Nd:YAG, in Dr. Ortiz's experience, insurance generally only covers skin cancer (when using a destruction code) and port wine stains.

"I think it brings attention to the fact that we need to work on getting more insurance coverage for these medical treatments. Even though we're using lasers, it's not [for] a cosmetic indication." ◈

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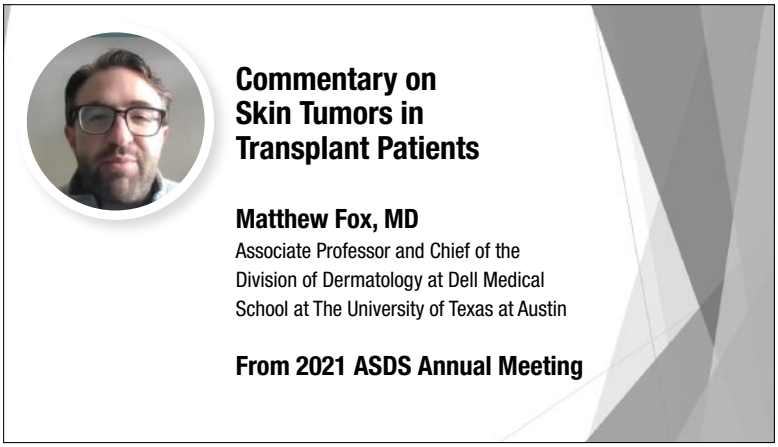
> One of the things that I use it for is thicker port wine stains—port wine stain birthmarks"

> Because the 1064 nm Nd:YAG has a longer wavelength, it bypasses epidermal melanin making it safe for all skin types, including types 5 and 6….

Skin Cancer in Organ Transplant Patients

With Matthew Fox, MD

Dr. Matthew Fox discusses skin cancer incidence among transplant patients and the dermatologist's role on the patient team.



WATCH: https://vimeo.com/662623716/8b859025ed

"We as dermatologists know that any type of immunosuppression—particularly among those patients who've had immune suppression related to receiving an organ transplant—really raises the risk of skin cancer and can quite dramatically raise that risk for some types of skin cancer," said Matthew Fox, MD, who was Director of the Transplant Tumor Board at the 2021 American Society for Dermatologic Surgery (ASDS) Annual Meeting.

Session speakers included Bryan Carroll, MD, PhD; Sean Christensen, MD; Thuzar M. Shin, MD, PhD; and Mary Stevenson, MD.

"It's estimated, according to some studies, that 20 years out after transplant as many as 80% of patients will have developed at least one skin cancer."

About 1 in 5 Americans will develop skin cancer in their lifetime, but those patients who have had an organ transplant and are immunosuppressed have an up to 65 times higher incidence of squamous cell carcinoma, approximately 10 times higher incidence of basal cell carcinoma, and triple the incidence of melanoma, said Dr. Fox.

"So it's an important part to consider when we're doing skin exams… to know if a patient has had a transplant, if they've been immu-

nosuppressed, and knowing the risk for skin cancer development."

Importantly, treatment of transplant patients can be complex and involves a multi-team effort, including transplant surgeons, ancillary medical staff, and a dermatologist, said Dr. Fox.

"Our membership on the transplant team is to help with risk assessment and then, obviously, prevention and treatment of cancer that may develop."

It's an important role, emphasized Dr. Fox.

"A lot of these patients have very complicated medical histories. The skin cancers they grow can be very difficult to treat, require a little bit of finesse, and shared decision making with other specialties."

In the ASDS session, Dr. Carroll, Case Western School of Medicine, Cleveland, Ohio, discussed transplant team citizenship and the role dermatologists play.

"Dr. Carroll in our session talked a lot about keeping lines of communication open, giving really clear assessments and recommendations. If we're seeing a lot of skin cancers develop in our patients, we'll ask the transplant team to consider changing the immunosuppression regimen to help lower the risk of skin cancer.… Our job is to provide input as to their risk on the skin cancer side."

Dr. Stevenson, NYU Langone Medical Center, New York City, discussed field treatment for these patients and trying to prevent skin cancer, said Dr. Fox.

"There's some interesting new data, and I learned a lot from Dr. Stevenson in our session about this—[on] combining topical fluorouracil with topical vitamin D analogs like calcipotriene as field treatment for these patients."

Dr. Fox pointed out that this treatment combination is appropriate for both transplant and nontransplant patients with skin fields (eg, actinic keratoses) that are at risk.

Importantly, treatment of transplant patients can be complex and involves a multi-team effort, including transplant surgeons, ancillary medical staff, and a dermatologist.

There are also new agents on the horizon, he said.

"There's data that's come within the last few years about taking [oral] nicotinamide to reduce risk of squamous cell carcinoma."

Dr. Shin, Penn Medicine, Philadelphia, Pa., and Dr. Christensen, Yale School of Medicine, New Haven, Conn., talked about more advanced cases, the dermatologist's approach, and relevance to multidisciplinary care.

Ultimately, while the dermatologist has an important role on the transplant patient team, said Dr. Fox, the overall key to patient care is making decisions as a team.

"I think it's good for dermatologists to realize how important we can be on a multidisciplinary team.… I'd also point dermatologists to a really great group… the International Immunosuppression Transplant Skin Cancer Collaborative (ITSCC), which has some really great resources for patients and dermatologists." ◈

It's estimated, according to some studies, that 20 years out after transplant as many as

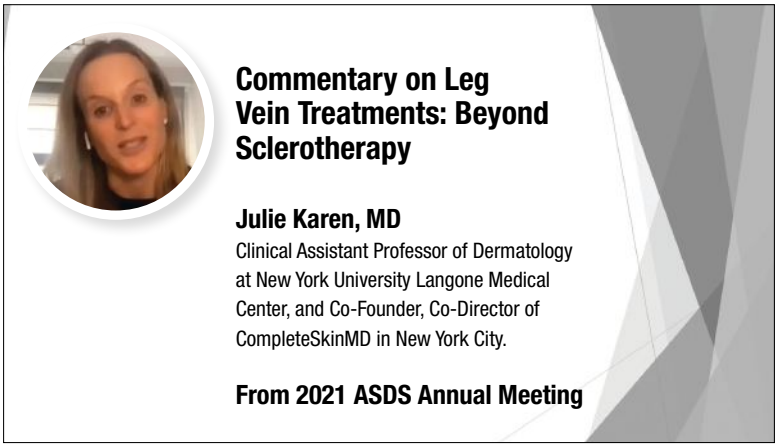
80%

of patients will have developed at least one skin cancer."

Spider Veins or Venous Insufficiency?

With Julie Karen, MD

Dr. Julie Karen discusses the signs and symptoms of venous insufficiency and tips for successful leg vein treatment.



WATCH: https://thedermdigest.com/uncategorized/spider-veins-or-venous-insufficiency

"When someone does not have underlying venous insufficiency and they just have spider veins and reticular veins… very often those can be very readily treated with sclerotherapy. Sclerotherapy has become an integral component of our residency training programs," said Julie Karen, MD, who presented "Beyond Sclerotherapy" as part of the Vein Treatment session at the 2021 American Society for Dermatologic Surgery (ASDS) Annual Meeting.

"There's a quick learning curve, it's easy to use, it can be fun to do, and very gratifying."

However, sclerotherapy isn't always the appropriate treatment. Key to effective leg vein treatment is identifying possible underlying venous insufficiency, said Dr. Karen.

"First and foremost, you should suspect that there could be underlying venous insufficiency, meaning backward flow within the vessels of our legs, that puts pressure on the visible veins and that would preclude effective treatment with sclerotherapy."

Symptoms of venous disease include aching, swelling, cramping, edema, fatigue, heaviness, and restless legs, said Dr. Karen.

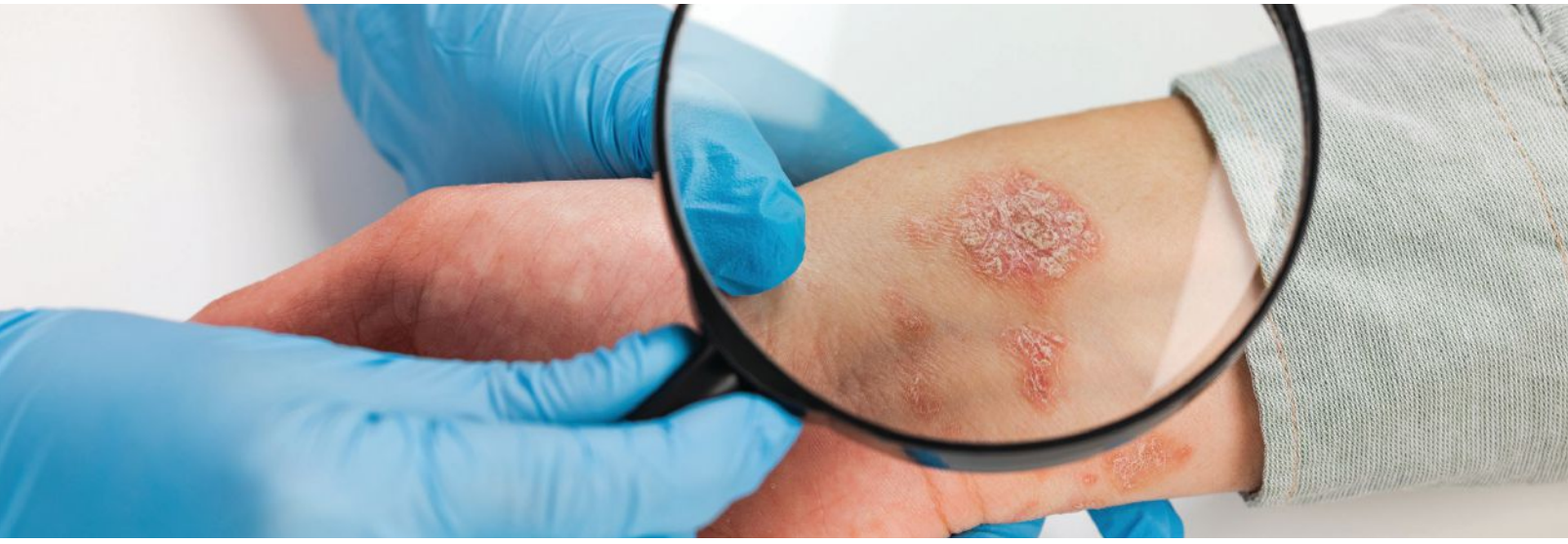
"If you have a patient who is reporting symptoms of venous disease… any or all of those symptoms can indicate an underlying venous

continued on page 34

THE Dermatology Digest PRESENTS

Mild to Moderate Psoriasis, The Unmet Need

VIDEO EDUCATION SERIES | NOVEMBER 2021– JANUARY 2022



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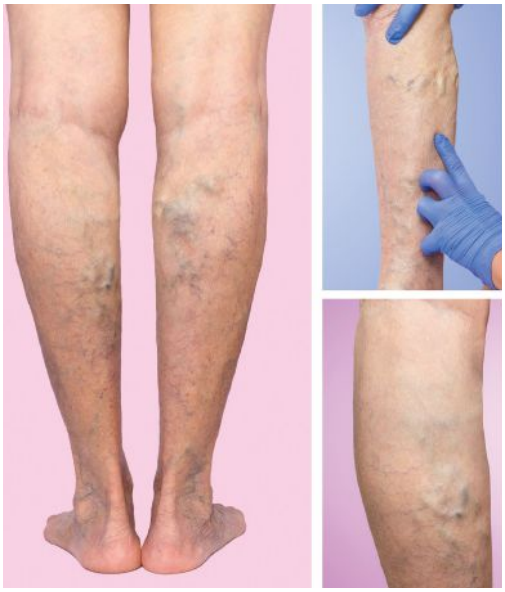
November 2021 — Part 1: Overview of the Pathogenesis of Psoriasis and Comorbidities

December 2021 — Part 2: Current Treatment Options and Unmet Needs

January 2022 — Part 3: Future Landscape for mild-mod Psoriasis

continued from page 32

> Symptoms of venous disease include aching, swelling, cramping, edema, fatigue, heaviness, and restless legs."



condition. If you suspect it, you want to either perform an ultrasound or refer the patient for an ultrasound."

According to Dr. Karen, another sign of an underlying venous problem is bulging varicose veins in specific zones of the saphenous system.

"Patients may not report symptoms often because these symptoms are insidious. They have occurred over many years and decades and patients have acclimated to their symptoms and they may have learned to ignore them."

The great saphenous vein begins in the medial ankle, continues up the medial calf and thigh, ending in the groin area where it meets the femoral vein.

"If someone has bulging veins or many veins in that medial distribution, you want to consider that maybe they have great saphenous venous insufficiency, and if you just try to patch up the visible veins with sclerotherapy, you're not going to have success."

Another system to consider during assessment is the small saphenous venous system. This system begins at the posterior lateral aspect of the ankle, continues up the midline of the posterior calf, and ends at or around the knee, said Dr. Karen.

"If someone has a bulging vein on the posterior aspect of the leg, you might want to suspect that they need to get an ultrasound because perhaps they have venous insufficiency."

Other signs of venous insufficiency that may warrant an ultrasound include a strong family history of venous disease, poor sclerotherapy response, and previous venous surgery, said Dr. Karen.

"That's the most important thing—who might need underlying investigation; who might need, therefore, endovenous laser ablation to treat those underlying problems or even just ultrasound guided sclerotherapy injections to treat the feeding vessels that are causing the visible concerns."

Although infrequently required, alternative treatments are available for patients who are not good candidates for sclerotherapy.

"If you have a patient who is terrified of needles [and] faints every time you go near them, someone who gets ocular migraines every time you inject their vessels, someone who just isn't getting better with sclerotherapy and [you] rule out underlying disease, sometimes then we will utilize percutaneous lasers, such as the Nd:YAG or the pulsed dye laser."

Although lasers are not as effective as sclerotherapy, which is considered the gold standard treatment, they can be helpful for some patients, said Dr. Karen.

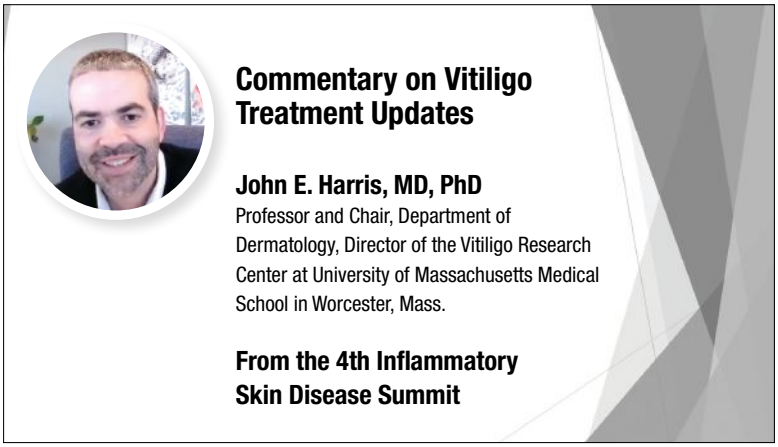
Because leg veins are often a patient's primary concern, Dr. Karen encourages other dermatologists to attend one of the hands-on sessions offered at educational meetings such as the ASDS Annual Meeting or AAD Annual Meeting.

"[Leg vein treatment] can provide tremendous relief and satisfaction for patients and translate into a very rewarding patient-physician relationship." ◈

Vitiligo Treatment Updates

With John E. Harris, MD, PhD

Dr. John Harris discusses the current and future landscape for vitiligo treatment.



WATCH: https://thedermdigest.com/video/vitiligo-treatment-updates

"We've been using the same [vitiligo] treatments for about 3400 years: sunlight and light-activated chemicals, while now we use narrowband UVB, which is a small improvement," said John E. Harris, MD, PhD, who discussed vitiligo treatment updates at the 4th Inflammatory Skin Disease Summit.

"We have good treatments for vitiligo, but they're really cumbersome. They take a long time. Patients have to really commit to 12 to 14 months of treatment to get decent improvement."

However, research over the past decade into what causes vitiligo has led to new treatment opportunities, said Dr. Harris. There are two signaling cytokine pathways that can be targeted for vitiligo: JAK inhibitors for interferon gamma signaling and biologics to target IL-15 signaling.

"A phase II and then phase III clinical trial have now been conducted using topical ruxolitinib [Opzelura] to treat vitiligo, and both showed that it was very effective....[1] The FDA has approved it for atopic dermatitis and now we're hoping in the next few months it will be approved for vitiligo. That would be the first FDA-approved treatment for vitiligo, ever."

In terms of biologics, a clinical trial is currently

> A phase II and then phase III clinical trial have now been conducted using topical ruxolitinib [Opzelura] to treat vitiligo, and both showed that it was very effective.... The FDA has approved it for atopic dermatitis and now we're hoping in the next few months it will be approved for vitiligo. That would be the first FDA-approved treatment for vitiligo, ever."

recruiting patients to address disease relapse, which is about 40% within a year of stopping any treatment, said Dr. Harris.

"We wanted to know why—why does vitiligo come back? And importantly, why does it come back in exactly where it was before?"

According to Dr. Harris, they found that resident memory T cells form within vitiligo lesions.

"You can take a JAK inhibitor or any other treatment and turn off these cells, and everything gets better. But then if you stop the treatment, they're still there. They wake back up and reinitiate everything."

Those memory T cells require IL-15 signaling for long-term maintenance and survival, said Dr. Harris.

"When we blocked IL-15 signaling, not only did vitiligo get better in a mouse model, but those… memory T cells were erased from the skin. Short-term treatment gave us long-term effects. We're hoping that blocking IL-15 with an antibody… will last not just for a short period of time but actually give a durable, long-term response."

In their research, Dr. Harris and colleagues also have found hundreds of other activated pathways to potentially target for vitiligo treatment.[2]

"We're pursuing those. There's some promise that maybe someday we'll have even better [treatments]. Could the cure for vitiligo be in that data somewhere? We're hoping so."

According to Dr. Harris, treatments under consideration include a bi-specific antibody and RNA interference (RNAi).

"We know we can treat psoriasis [and] atopic dermatitis with an antibody. We showed some data… [with] a bi-specific antibody, where one antibody targets two different things. We can bring the treatment into the skin, tether it there, and create a high local concentration that might be both safer and have higher efficacy for patients."

RNAi may also be an option for treating vitiligo and other inflammatory skin diseases, said Dr. Harris.

"It's a new way to turn off proteins in different tissues, and we found a way to deliver this specifically to the skin."

Despite all these up-and-coming treatments, Dr. Harris has a key message for dermatologists who may believe they do not currently have viable treatment options for their vitiligo patients.

"There's plenty you can do even now with the tools that we have, the drugs, the treatment approaches.... It's just cumbersome and difficult and not everybody has access."

Current off-label treatment options include tofacitinib (Xeljanz XR) and ruxolitinib, said Dr. Harris.

"Oral tofacitinib works for vitiligo. It's tough to get because it's not FDA approved for vitiligo. It's very expensive. So, trying to get that approved for use in patients can be difficult, although not impossible."

The oral JAK inhibitor also recently received a black box warning for safety concerns.

According to Dr. Harris, he has topical ruxolitinib compounded at a compounding pharmacy.

"I've used [ruxolitinib] over the last few years. But as soon as that gets FDA approved for vitiligo, we'll have it from the pharmacy and be able to prescribe it on label which would be exciting." ◈

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Neurotoxins for Non-Cosmetic Use

With Anthony Benedetto, DO, FACP

Dr. Anthony Benedetto discusses therapeutic uses of botulinum toxin for indications including hyperhidrosis, blepharospasm, and migraine.

WATCH: https://thedermdigest.com/video/neurotoxins-for-non-cosmetic-use

"I use botulinum toxins… for cosmetic reasons, but there's a whole host of reasons why I use them for therapeutic purposes, from blepharospasm [and] migraine headaches to hyperhidrosis," said Anthony Benedetto, DO, FACP, who presented "Dermatologic Non-Cosmetic Use of Neurotoxins" at the XIII International Congress of Dermatology (ICD 2021).

Of these three non-cosmetic indications, Dr. Benedetto most frequently uses onabotulinumtoxinA (BOTOX, Allergan) for hyperhidrosis in his practice.

"I have treated patients with hyperhidrosis on anywhere from the scalp to the feet and every skin area in between that has eccrine glands that sweat," said Dr. Benedetto.

Dr. Benedetto uses incobotulinumtoxinA (Xeomin, Merz) for other reasons.

Both are type-A toxins and may be used to treat hyperhidrosis, blepharospasm, and as prophylaxis for migraine headaches.

- OnabotulinumtoxinA is FDA approved for severe axillary hyperhidrosis, blepharospasm, and headache prophylaxis in adult patients with chronic migraines.
- IncobotulinumtoxinA is FDA approved for blepharospasm, chronic sialorrhea, limb

spasticity, and cervical dystonia.

But, Dr. Benedetto cautioned, botulinum toxin is best used to treat smaller, finite areas of excessive sweating rather than those that are more extensive.

"…you can only give so much botulinum toxin in one sitting. If there's focal or localized areas of sweating, that's where I use it—the face, the scalp, the inguinal area."

For treating excessive sweating on larger body surface areas, Dr. Benedetto said oral medication is a better option.

Treatment of hyperhidrosis may be covered by insurance for hyperhidrosis of the palms or axilla, said Dr. Benedetto. In his experience, treatment for migraine headaches, blepharospasm, and hemifacial spasm may also be covered. Coverage is determined by individual healthcare policy and medical necessity when the appropriate criteria are met.

"By and large, the patients who are being treated for those problems have coverage. If they don't have coverage, it's expensive… there's only a few that can afford it and I give them a little bit of a break."

Botulinum toxin can also be used before or after excisional surgery to improve the appearance of facial scars, particularly in areas of high tension including the forehead and around the periorbital area, said Dr. Benedetto.

"By reducing the vector of tension across the scar, it also helps reduce the tendency for hypertrophic scars, thick scars, [and] red scars. Reducing the redness and tension around a scar helps to diminish inflammation, inhibit excess fibroblast formation, and lessen the tendency for a thick scar."

Despite research that shows the clinical benefit of using botulinum toxin injections postop to improve the appearance of scars, this treatment approach has yet to become routine, said Dr. Benedetto.

"I think one of the main reasons is that it's not really covered by insurance and it can be relatively expensive."

There may also be potential for using diluted botulinum toxin intradermally to treat the redness associated with rosacea, said Dr. Benedetto.

"MicroBotox injections are very, very diluted with the amount of toxin. They have to be injected superficially and they have to be injected in multiple areas."

This technique delivers less muscle relaxing and wrinkle change, but the wide coverage of the face is said to have a vasosuppressive effect, which minimizes the tendency to flush, said Dr. Benedetto, who learned the technique in Thailand from a well-known dermatologist.

"It's something that's kind of impractical, can be a little painful, and it has to be done every two weeks or three weeks—three or four or five times—then the skin does relax. It's an intradermal [injection] so we're not affecting the deeper muscles, so it doesn't change the expression."

Although Dr. Benedetto admitted that he doesn't perform the microBotox technique to treat rosacea, he uses a similar injection approach for treating hyperhidrosis of the face.

"I do similar kinds of injections when I do hyperhidrosis of the face… it's a low dose… [across] the center of the face to the top of the nose, around the lips, the lateral face, [and] even in the forehead."

The intradermal technique is important to avoid relaxing the levitators and depressors around the mouth, which can result in abnormal smiling and/or drooling.

"With deep injections … you'll get abnormal smiling. You'll get the inability to pucker and tighten the lips, so you'll have drooling and you won't be able to drink. You can't go deep. You have to go very intradermally…. It's a highly diluted dose in multiple areas and in areas where you should not be injecting [deep]." ◈

"… botulinum toxin is best used to treat smaller, finite areas of excessive sweating rather than those that are more extensive."

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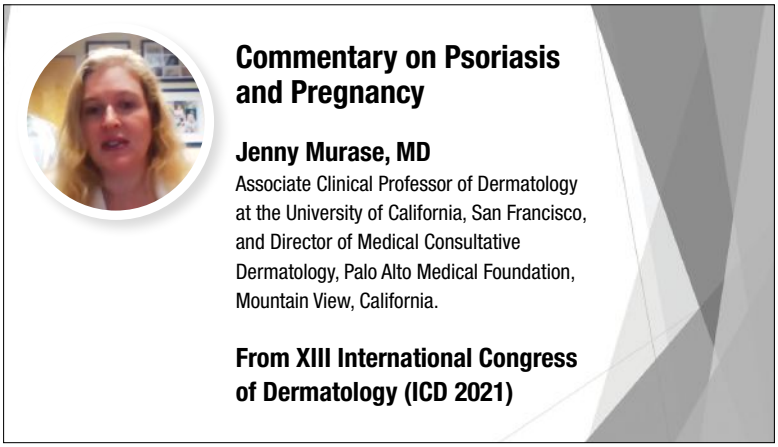
Tips for Treating Psoriasis in Women

With Jenny Murase, MD

Dr. Jenny Murase discusses treatment options and management for patients with psoriasis who are or may become pregnant.



WATCH: https://thedermdigest.com/video/tips-for-treating-women-with-psoriasis

"As we know, psoriasis is a chronic inflammatory skin disease, and so, whenever a patient is on therapy long term, you have to assume that they might become pregnant on a therapy you've prescribed them," said Jenny Murase, MD, who presented "Psoriasis and Pregnancy" at XIII International Congress of Dermatology (ICD 2021).

"For patients who are pregnant, there are good options where they can be very comfortable throughout their pregnancy and have a safe delivery if they select therapies that are safe during pregnancy."

The problem is, said Dr. Murase, patients on psoriasis therapies who are of childbearing age rarely seek out physician guidance before they become pregnant.

"It's very common for people to become pregnant without having a discussion [with their physicians] and be on these chronic therapies. So really, the onus is on us as dermatologists to initiate the conversation and make sure that if a patient does become pregnant on the therapy, they know the impact of the therapy on a potential fetus."

According to Dr. Murase, light therapy is very safe during pregnancy. However, studies show a reduction in folic acid levels over time

for patients on long-term narrowband UVB phototherapy to treat psoriasis, she said.

"So it's important to make sure that patients that are on light therapy in their childbearing years are on a prenatal vitamin, taking at least 1 mg folic acid a day."

Of the available biologics, anti-TNF-alpha agents have the most safety data to support use during pregnancy, said Dr. Murase. In particular, certolizamab (Cimzia) has been studied extensively in pregnant and breastfeeding women because it is fragment crystallizable (Fc)-free, preventing antibody transference across the placenta.

"There are more supportive data for the TNF agents than IL-23 and IL-17 agents, so I personally feel more comfortable going with what agents have the most data. And I think certolizumab would be a very good choice because then you don't have to worry about transitioning in the second or third trimester."

Other anti-TNF agents that do cross the placenta (eg, infliximab, adalimumab) can cause immunosuppression in the fetus, said Dr. Murase. In which case, "The first six to nine months of life live vaccines are not recommended."

Although data are limited, etanercept is another TNF biologic that has a low transplacental rate, she said.

Notably, pregnancy itself can be therapeutic, said Dr. Murase.

"I initially became interested in saying this over 20 years ago because when I was starting medical school, the chair of the department brought in a patient who had very severe psoriasis. She was just covered from head to toe. He asked the patient about her pregnancies, and she said the only three times in her life that she was completely cleared was during her pregnancies."

According to Dr. Murase, about 50% of patients

experience an average of 80% resolution of skin lesions during pregnancy.

"It can be a very dramatic improvement and they may not need therapy during pregnancy, or you can reduce the frequency that you're even administering therapy."

However, postpartum, two-thirds of these patients will experience a return to baseline psoriasis. And that means having a plan to avoid Koebnerization of the nipples for those new mothers who intend to breastfeed, said Dr. Murase.

"If the nipples Koebnerize, that can be very painful. So in order to prevent that Koebnerization, you want the nipples [and] the skin to be in as good shape as possible prior to delivery."

Dr. Murase also pointed out that the ABCDX classifications are no longer used to describe risk of using psoriasis therapies in pregnant or lactating women.

"That's been changed within the past few years with the Pregnancy and Lactation Labeling Rule. So we don't use those categories that dermatologists have used for a very long time… instead, it's narrative-based, where you're actually giving specific risks for medicine." ◈

Of the available biologics, anti-TNF-alpha agents have the most safety data to support use during pregnancy.

About

50%

OF PATIENTS

experience an average of

80%

RESOLUTION OF SKIN LESIONS

during pregnancy.

What's New, What's Next in Technology

With Daniel M. Siegel, MD

Dr. Daniel Siegel discusses technology, including legalities and current and near-future innovations.

WATCH: https://thedermdigest.com/uncategorized/whats-new-whats-next-in-technology

"When the first digital cameras came out, I remember at a meeting in 1998 or 1999 holding up a Logitech, and I said, based on the improvements from generations 1 and 2, by 2010 nobody's going to use film anymore. People thought I was crazy," said Daniel M. Siegel, MD, who presented "What's New and Hot in Technology" at the 2022 Winter Clinical Dermatology Conference.

"With the advent of… the iPhone in 2007, suddenly you had an easy-to-use way to take images that were high quality, and the quality of those images, when projected, was as good as anything you could do with 35-mm slide in terms of the perception of the viewer."

Passionate about all things tech, Dr. Siegel said today's top of the line phones for taking quality images are the iPhone 13, the Pro, the Pro Max, and the Samsung Galaxy S21 Ultra.

Superior phone cameras and ease of use can also get you into trouble, cautioned Dr. Siegel. HIPAA can become an issue.

"Residents tend to use their cell phone. And when you are using your cell phone for taking pictures of patients, if you lose your cell phone… you could lose your job."

When using a camera phone for patient photos, Dr. Seigel advises two methods of security: using a failsafe phone login and/or a HIPAA

compliant app.

"Instead of having the [standard] four-digit passcode, you can have a complex phrase that could [for example] be your childhood nickname and the name of your best friend and you substitute 1s for Ls."

Dr. Siegel uses an online password manager only accessible with a creative and complex password that would be meaningless to anyone else.

In terms of HIPAA compliant apps, PicSafe, a cross platform photo vault, allows physicians to remain HIPAA compliant and is made in America. Dr. Siegel believes PicSafe may minimize backdoor access risk.

"But most importantly… you need to make sure that even if you found an app that is HIPAA compliant… you still need to check with your institutional compliance officer, or HIPAA office."

Nanotechnology

The CDC defines nanotechnology as "the manipulation of matter on a near-atomic scale to produce new structures, materials, and devices."

Both the Pfizer and Moderna vaccines depend on nanotechnology, making this "the biggest nanotech topic in the past 18 months," said Dr. Siegel.

Specific to the dermatology specialty, Greenway Therapeutix has nanotechnology in development designed to deliver cannabinoids for the treatment of inflammation, said Dr. Siegel, who is the company's Chief Scientific Officer.

"Most cannabinoids are sticky… so if you can entrap CBD inside a short-term lipid envelope at 50 nm, that can slip right down hair follicles and appendages and penetrate really well."

AI Technology

Once referred to as "artificial intelligence," today AI is more accurately known as "augmented intelligence," said Dr. Siegel.

The AI that we're looking at, for the most part, is primitive. It's all primitive. It's machine learning. In other words, it's not autonomous thought."

The benefit to humankind, he said, is that machines can do some things more efficiently and accurately than we can.

"For instance, they can take larger amounts of data and find inter-relationships much better than the average person can."

SkinVision, DermTech, and MetaOptima are among those companies that have AI technology with machine learning algorithms for stratifying malignancy risk in pigmented

Passionate about all things tech, Dr. Siegel said today's top of the line phones for taking quality images are the iPhone 13, the Pro, the Pro Max, and the Samsung Galaxy S21 Ultra.

SkinVision, DermTech, and MetaOptima are among those companies that have AI technology with machine learning algorithms for stratifying malignancy risk in pigmented lesions, said Dr. Siegel. These devices function as early screening tools, which offer benefit to both the dermatologist and patient in terms of time and treatment.

lesions, said Dr. Siegel. These devices function as early screening tools, which offer benefit to both the dermatologist and patient in terms of time and treatment.

"I'd rather have someone come in who has a defined problem and then I can make the final judgment to whether it needs [treatment] or not."

In another AI application, Brian Kim, MD, and Dina Katabi, PhD, have designed a technology to examine chronic itch and the effectiveness of itch therapies in children. The technology is a wearable system that tracks motion and breathing at night.

"There's no video to relay. It just pairs wireless tech and machine learning and [researchers] will be able to quantify and see what's working. Great for studies. Great for parents. I think there's a lot of potential opportunity there."

Electrical Technology

Electrical technology is another option in the dermatologist's skin cancer detection toolbox.

Electrical Impedance Spectroscopy (EIS) technology (Nevisense; Scibase) is commercially available and uses electrical measurements in the skin for non-visual malignant melanoma detection.

According to the company's website, "EIS is sensitive to changes in cellular structure, cellular orientation, cell sizes and cell types – all of which are similar to those on which a histopathologist would base his or her diagnosis."

Another electrical technology (NovaScan) is currently under investigation for differentiating between benign and malignant cells with Cole Relaxation Frequency, said Dr. Siegel.

"If you send an electric current through a cell, the cell contracts, and then it starts to relax. Malignant cells and benign cells and every tissue studied so far—breast, skin, gut, lungs—the graphs [don't have bimodal distribution] overlap…. It's amazingly sensitive—amazingly specific. And this will probably wind up on the market for the next year or two."

Of all the technologies Dr. Siegel has presented on over the years, each shares a common purpose.

"I like to give talks that basically help you look forward…. I try to open people's eyes to what could be because you just never know which technology you may look at and find another use [for]. You may have that a-ha moment, and it's fascinating." ◈

DISCLOSURE

Dr. Siegel is a consultant for SkinVision, DermTech, and Scibase.

HOW YOU PRESCRIBE TODAY, REDEFINES THEIR TOMORROW

The safety and efficacy of ORACEA® (doxycycline, USP) 40 mg* Capsules in the treatment of inflammatory lesions (papules and pustules) of rosacea was evaluated in two randomized, placebo-controlled, multi-centered, double-blind, 16-week Phase 3 trials involving 537 subjects (total of 269 subjects on ORACEA Capsules from the two trials) with rosacea (10 to 40 papules and pustules and two fewer nodules.)^[1,2]

Mean change in lesion count ORACEA Capsules vs Placebo : Study 1 -11.8 vs -5.9, Study 2 -9.5 vs -4.3

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*30 mg immediate release and 10 mg delayed release beads

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†ORACEA Capsules did not include symptoms of nausea, diarrhea, vomiting or abdominal pain[1,2]

NO EVIDENCE OF BACTERIAL RESISTANCE IN A 9-MONTH STUDY[8]

Important Safety Information

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*30 mg immediate release and 10 mg delayed release beads

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Please see brief summary of full Prescribing Information on next page.

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BRIEF SUMMARY
This summary contains important information about ORACEA (Or-RAY-sha) Capsules. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start taking ORACEA Capsules. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about ORACEA Capsules. For full Prescribing Information and Patient Information please see the package insert.

WHAT IS ORACEA CAPSULES?
ORACEA Capsules are a tetracycline class medicine. ORACEA Capsules are a prescription medicine to treat only the pimples or bumps (papules and pustules) caused by a condition called rosacea. ORACEA Capsules do not lessen redness caused by rosacea. ORACEA Capsules should not be used for the treatment or prevention of infections. It is not known if ORACEA Capsules are effective for use for longer than 16 weeks, safe for use longer than 9 months, or safe and effective in children. ORACEA Capsules should not be used in infants and children less than 8 years of age because it may cause stained teeth in infants and children.

WHO SHOULD NOT TAKE ORACEA CAPSULES?
Do not take ORACEA Capsules if you are allergic to doxycycline or other medicines in the tetracycline class. Ask your doctor or pharmacist for a list of these medicines if you are not sure.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING ORACEA CAPSULES?
Before you take ORACEA Capsules tell your doctor if you:
- have kidney problems.
- have liver problems.
- have diarrhea or watery stools.
- have vision problems.
- have had surgery on your stomach (gastric surgery).
- have or had a yeast or fungal infection in your mouth or vagina.
- have any other medical condition.
- are pregnant or planning to become pregnant. ORACEA Capsules may harm your unborn baby. Taking ORACEA Capsules while you are pregnant may cause serious side effects on the growth of bone and teeth of your baby. Stop taking ORACEA Capsules and call your doctor right away if you become pregnant while taking ORACEA Capsules.
- are breastfeeding or plan to breastfeed. ORACEA Capsules can pass into your breast milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take ORACEA Capsules. You and your doctor should decide if you will take ORACEA Capsules or breastfeed. You should not do both.

You should not take ORACEA Capsules if you are male with a female sexual partner who plans to become pregnant at any time while you are being treated with ORACEA Capsules.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ORACEA Capsules and other medicines can affect each other causing serious side effects.

Especially tell your doctor if you take:
- birth control pills. ORACEA Capsules may reduce the effectiveness of birth control pills. Talk to your doctor about what types of birth control you can use to prevent pregnancy while taking ORACEA Capsules.
- a blood thinner medicine
- a penicillin (antibacterial medicine).
- proton pump inhibitors or antacids that contain aluminum, calcium, or magnesium.
- products containing iron or bismuth subsalicylate.
- a medicine taken by mouth that contains isotretinoin or acitretin.
- a medicine to treat seizures, such as carbamazepine or phenytoin.

Ask your doctor or pharmacist for a full list of your medicines, if you are not sure. Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ORACEA CAPSULES?
ORACEA Capsules may cause serious side effects, including:
- **Harm to an unborn baby. See "What should I tell my doctor before taking ORACEA Capsules?"**
- **Permanent teeth discoloration.** ORACEA Capsules may permanently turn a baby or child's teeth yellow-grey-brown during tooth development. ORACEA Capsules should not be used during tooth development. Tooth development happens in the last half of pregnancy, and from birth to 8 years of age. See "What should I tell my doctor before taking ORACEA Capsules?"
- **Intestine infection (pseudomembranous colitis).** Pseudomembranous colitis can happen with most antibiotics, including ORACEA Capsules. Call your doctor right away if you get diarrhea or bloody stools.
- **Immune system reactions including a lupus-like syndrome, hepatitis, and inflammation of blood or lymph vessels (vasculitis).** Stop taking ORACEA Capsules and tell your doctor right away if you get joint pain, fever, rash or body weakness.
- **Discoloration (hyperpigmentation).** ORACEA Capsules can cause darkening of your skin, scars, teeth, gums, nails, and whites of your eyes.
- **Benign intracranial hypertension, also called pseudotumor cerebri.** This is a condition where there is high pressure in the fluid around the brain. The swelling may lead to vision changes and permanent vision loss. Stop taking ORACEA Capsules and tell your doctor right away if you have blurred vision, vision loss, or unusual headaches.

The most common side effects of ORACEA Capsules include: soreness in the nose and throat, diarrhea, sinus infection, stomach (abdominal) bloating or pain, fungus infection, high blood pressure (hypertension), flu-like symptoms, and change in certain blood tests.

Tell your doctor if you have any side effect that bothers you or does not go away. These are not all the possible side effects of ORACEA Capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to GALDERMA LABORATORIES, L.P. at 1-866-735-4137.

HOW SHOULD I TAKE ORACEA CAPSULES?
- Take ORACEA Capsules exactly as prescribed by your doctor. Taking more than your prescribed dose may increase your chance of side effects, including the chance that bacteria will become resistant to ORACEA Capsules.
- Take ORACEA Capsules 1 time a day in the morning on an empty stomach.
- You should take ORACEA Capsules at least one hour before or two hours after a meal.
- Take ORACEA Capsules with enough fluid to completely swallow the capsule and to lower your risk of getting irritation or ulcer in your esophagus. Your esophagus is the tube that connects your mouth to your stomach.
- If you took too much ORACEA Capsules, call your doctor right away.
- Your doctor may do blood tests during treatment with ORACEA Capsules to check for side effects.

WHAT SHOULD I AVOID WHILE TAKING ORACEA CAPSULES?
- Avoid sunlight or artificial sunlight, such as a tanning booth or sunlamp. You could get severe sunburn. Use sunscreen and wear clothes that cover your skin while out in sunlight.

HOW SHOULD I STORE ORACEA CAPSULES?
- Store ORACEA Capsules at room temperature between 59ºF to 86ºF (15ºC to 30ºC).
- Keep ORACEA Capsules in a tightly closed container.
- Keep ORACEA Capsules inside container and out of light.

Keep ORACEA Capsules and all medicine out of the reach of children.

GENERAL INFORMATION ABOUT ORACEA CAPSULES
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take ORACEA Capsules for a condition for which it was not prescribed. Do not give ORACEA Capsules to other people, even if they have the same symptoms you have. It may harm them.

This Brief Summary summarizes the most important information about ORACEA Capsules. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information that is written for health professionals.

WHAT ARE THE INGREDIENTS IN ORACEA CAPSULES?
Active ingredient: doxycycline. Inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT ORACEA CAPSULES?
- Talk to your doctor or pharmacist
- Go to **www.oracea.com** or call **1-866-735-4137**

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REFERENCES

1. ORACEA [package insert]. Fort Worth, TX: Galderma Laboratories, L.P.;2013. **2.** Del Rosso JQ, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. J Am Acad Dermatol. 2007;56(5):791–802. **3.** Del Rosso JQ, et al. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. J Drugs Dermatol. 2008;7(8):573-576. **4**. Bhatia N. ORACEA 40 mg capsules for papulopustular rosacea. The Dermatologist. 2013;6(21s):1-4. Available at: https://pdfs.semantic scholar.org/363e/66311811307ccfdc9e9d8bd8b594bdaf4254.pdf. Accessed: October 2019. **5.** Theobald K, et al. Anti-inflammatory dose doxycycline (40 mg controlled-release) confers maximum anti-inflammatory efficacy in rosacea. Skinmed. 2007;6(5):221-226. **6.** Wise RD. Sub microbial doxycycline and rosacea. Compr Ther. 2007;33(2):78-81. **7.** Etchegaray JP, Wagner N, Shah MS, Difalco RJ, inventors; Galderma S.A., Cerovene, Inc. assignees. Doxycycline formulations, and methods of treating rosacea. US Patent 8,652,516 Bl. February 18, 2014. **8.** Preshaw PM, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planning in subjects with periodontal disease. J Periodontal. 2008;79(3):440-452.

A Dying Penis

With Ted Rosen, MD, FAAD

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

CASE HISTORY

A 45-year-old Black male with poorly controlled Type 1 diabetes and chronic renal disease presented to the Emergency Department with a three-week history of a gradually expanding and extremely painful penile lesion.

On the visual analog scale (VAS), his pain was assessed to be 9 out of 10. Aside from routine hemodialysis, the patient denied any recent medical procedures or instrumentation. A battery of tests was ordered, including a rapid plasma reagin (RPR), HSV-2 and HIV serologies, a CBC and complete metabolic panel, clotting studies, and an antinuclear antibody (ANA) and rheumatoid factor. The patient was appointed to see Urology Service and Dermatology the following day and was given oral cephalexin for presumed infection and opioid narcotics for pain.

Figure 1.

> Laboratory values obtained in the ED the previous day were negative or normal except: elevated calcium-phosphate product of 58 mg/dL (upper limits of normal 52.5), blood glucose of 212 mg/dL, creatinine of 3.4mg/dL and BUN of 48mg/dL.

On presentation the next day, the patient was diaphoretic due to discomfort but afebrile. He had a necrotic eschar covering virtually all of the glans penis and extending cephalad to involve the corona, the coronal sulcus and the distal penile shaft. (Figure 1)

Laboratory values obtained in the ED the previous day were negative or normal except: elevated calcium-phosphate product of 58 mg/dL (upper limits of normal 52.5), blood glucose of 212 mg/dL, creatinine of 3.4mg/dL and BUN of 48mg/dL. A plain abdominopelvic film was unrevealing. A CT scan (done without contrast) showed calcification in the internal iliac and internal pudendal arteries. The patient was admitted for further workup and treatment.

What does the patient have and what is his prognosis?

For more on this case, turn to page 48 ▸

continued from page 48

DISCUSSION

Calciphylaxis is a rare phenomenon, affecting about 1% of those with chronic renal insufficiency, especially those with diabetes as an etiology of the chronic kidney disease.

A small skin biopsy done just proximal to the edge of the eschar showed intraluminal calcium deposits within arterioles and prominent hyperplasia of the intima and media. Considering the underlying chronic renal disease and diabetes, the elevated calcium-phosphate product, the imaging results and the overall clinical picture, a diagnosis of penile calciphylaxis was made.

Although intravenous sodium thiosulfate, the drug of choice, was started almost immediately, the necrosis continued to progress and pain was essentially refractory to medical management. Therefore, a partial penectomy was performed. The patient stabilized and survived.

Calciphylaxis is a rare phenomenon, affecting about 1% of those with chronic renal insufficiency, especially those with diabetes as an etiology of the chronic kidney disease. Penile involvement is seen in only about 6% of all calciphylaxis cases, likely due to extensive collateral circulation protecting the male genitalia from ischemia. Penile calciphylaxis carries a grave prognosis: 50% to 65% mortality within 2.5 to 6.0 months despite medical or surgical intervention. Diagnosis is usually based on the constellation of clinical signs and symptoms in a patient at high risk due to underlying comorbidities. There is no specific diagnostic test. Imaging demonstrating extensive calcification in the blood vessels supplying the necrotic skin region is supportive of the diagnosis, but not necessary. Administration of warfarin, steroids, and vitamin D preparations may facilitate the development of calciphylaxis.

Therapy for penile calciphylaxis consists of intravenous sodium thiosulfate and debridement of necrotic tissue, along with meticulous metabolic support. Hyperparathyroidism may be present and should be treated with parathyroidectomy, although the survival rate is not statistically improved in some studies. Penectomy may be required for progressive disease, as in this case. ◈

By Ted Rosen, MD, FAAD

RECOMMENDED READING

- Gabel C, Chakrala T, Shah R, et al. Penile calciphylaxis: A retrospective case-control study. *J Am Acad Dermatol*. 2021;85(5):1209-1217. doi:10.1016/j.jaad.2020.05.042.
- Adler K, Flores V, Kabarriti A. Penile calciphylaxis: A severe case managed with partial penectomy. *Urol Case Rep*. 2020;34:101456. Published 2020 Oct 16. doi:10.1016/j.eucr.2020.101456.
- Lei GY, Tay KV, Hern Qi Chong C, Ho T. Penile gangrene from calciphylaxis is salvageable with intravenous sodium thiosulfate and early total parathyroidectomy. *Int J Surg Case Rep*. 2021;79:67-69. doi:10.1016/j.ijscr.2020.11.085.

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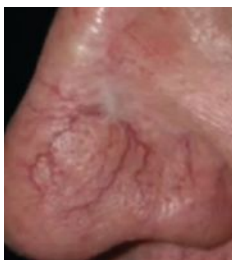
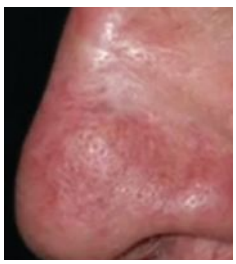

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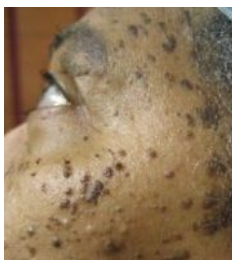
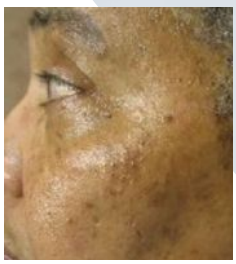

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