Innovations LEADS TO DERMATOLOGY

New treatment options for major conditions

Iya Petrou MD, Staff Correspondent

DEVELOPMENTS IN THE TREATMENT of numerous dermatologic diseases are providing much-needed options to patients with these conditions. New biologics and Janus kinase (JAK) inhibitors offer choices for an increasing list of diseases and conditions, including atopic dermatitis, alopecia areata, psoriasis, and more.

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Hello! Here at MJH Life Sciences®, we are in the middle of what we call conference season. Fall is a particularly flush time for medical meetings around the United States. With more than 60 medical brands under our rooftop—from dentistry to oncology to psychiatry—you can imagine that our associates are helping to keep the travel industry busy via hotel and airfare reservations for conferences in almost every region of the country.

For Dermatology Times®, the next few months bring some key meetings. The Fall Clinical Dermatology Conference (October 20-23) in Las Vegas, Nevada, will offer a 4-day accredited continuing medical education program providing updates on the diagnosis and treatment of a wide variety of conditions related to medical, surgical, and cosmetic dermatology. Session topics will include how to diagnose and manage patients with generalized pustular psoriasis, applying new technology in dermatology, therapeutic advances in the treatment of acne, and much more.

Then in November, our intrepid reporters head down to Miami, Florida, to cover the Society of Dermatology Physician Assistants 20th Annual Fall Dermatology Conference (November 17-20). Session topics will include dermoscopy, genodermatosis, hyperpigmentation, foundational information on acne and rosacea, and other compelling topics.

Come December, Revolutionizing Atopic Dermatitis (RAD) offers a virtual conference (December 11) to bring you all you need to know right now when it comes to diagnosing, treating, and managing atopic dermatitis. Here, clinicians will learn about new biologic therapies, the latest in treatment guidelines, mental health interventions, and other important updates on caring for patients with this skin disorder.

We look forward to being able to report live, as well as virtual, on these and other topical medical issues so that you can stay abreast of all that is newsworthy in dermatology.

Mike Hennessy Jr is the president and CEO of MJH Life Sciences®.
NOW AVAILABLE

RINVOQ®
upadacitinib

For adults and pediatric patients 12+ years with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

INDICATION
RINVOQ is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

SAFETY CONSIDERATIONS

SERIOUS INFECTIONS
Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include tuberculosis (TB), invasive fungal, bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

MORTALITY
A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase (JAK) inhibitor in a study comparing another JAK inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years of age with at least one CV risk factor.

MALIGNANCIES
Lymphoma and other malignancies have been observed in RINVOQ-treated patients. A higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, and lung cancer (in current or past smokers) was observed with another JAK inhibitor when compared with TNF blockers in RA patients. Patients who are current or past smokers are at additional increased risk.
Rapid Relief
EASI 75 measured at Week 16, and rates seen as early as Week 2\(^1\)
Reduced worst pruritus NRS ≥4 measured at Week 16, rates observed within 2 days after first dose\(^1\)

Durable Control
Co-primary endpoints EASI 75 and vIGA 0/1 controlled at Week 16\(^1\)
Response rates observed up to 52 weeks\(^2\)

Robust Results
90% skin improvement (EASI 90) measured at Week 16\(^1\)

Well-Studied Safety
Clinical trial experience in >9,000 patients since 2012 across 3 approved indications\(^1\)

Exceptional Access
Committed to AbbVie’s legacy of reliable access and patient services

SEEN HOW RINVOQ TAKES ON ATOPIC DERMATITIS AT RINVOQHCP.COM/AD

MAJOR ADVERSE CARDIOVASCULAR EVENTS
A higher rate of CV death, myocardial infarction, and stroke was observed with a JAK inhibitor in a study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years of age with at least one CV risk factor. Current or past smokers are at additional increased risk.

Thrombosis
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. A higher rate of thrombosis was observed with another JAK inhibitor when compared with TNF blockers in RA patients.

Hypersensitivity
RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients.

OTHER SERIOUS ADVERSE REACTIONS
Hypersensitivity Reactions (anaphylaxis and angioedema), Gastrointestinal Perforations, Laboratory Abnormalities (neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations), and Embryo-Fetal Toxicity.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events and Thrombosis, on the following pages of this advertisement.

Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.
SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:
- Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease.
- Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent infection prior to RINVOQ use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of overall mortality, including sudden CV death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC), lymphomas, lymphomas, and lung cancer in current or past smokers) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk.

With RINVOQ, consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In a large, randomized, postmarketing study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients who have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other CV risk factors. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing study comparing another JAK inhibitor to TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of thrombosis was observed with the JAK inhibitor. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated.

HYPERSENSITIVITY

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients. Severe hypersensitivity reactions, such as anaphylaxis and angioedema, were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. In these trials, many patients with RA were receiving background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count (ANC) <1000 cells/mm³). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm³. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm³ were reported in RINVOQ clinical studies. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm³. Evaluate at baseline and thereafter according to routine patient management.

Anemia

Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ clinical studies. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Lipids

Treatment with RINVOQ was associated with increases in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

Liver enzyme elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to placebo. Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

EMBRYO-FETAL TOXICITY

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

VACCINATION

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

HEPATIC IMPAIRMENT

RINVOQ is not recommended for use in patients with severe hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials (≥1%) were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, blood creatine phosphokinase increased, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, and influenza-like illness. Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any new changes in vision while receiving RINVOQ.

DOSAGE FORMS AND STRENGTHS

RINVOQ is available in 15 mg and 30 mg extended-release tablets.

Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.

EASI—Eczema Area and Severity Index, NRS—numerical rating scale, vGAt—Validated Investigator’s Global Assessment. EASI 75 is an improvement of at least 75% in EASI severity and EASI 50 is an improvement of at least 50% in EASI severity and extent. vGAt 4.0 is defined as clear or almost clear skin with at least 2 grades of reduction from baseline. Improvement in worst pruritus NRS ≥+4 is defined as an improvement (reduction) in worst pruritus NRS ≥+4 points.

Rinvoq® (Rin-Voke) (upadacitinib) extended-release tablets, for oral use

**INDICATIONS AND USAGE**

Rinvoq® (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have received prior treatment with one or more DMARDs.

**CONTRAINDICATIONS**

Rinvoq® is contraindicated in patients with a known history of serious skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis). Rinvoq® is also contraindicated in patients who have had a severe hypersensitivity reaction to Rinvoq® or any of its components.

**WARNINGS AND PRECAUTIONS**

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving Rinvoq®. The most frequent infection-related serious adverse events (SAEs) reported in clinical trials of Rinvoq® included cellulitis and pneumonia.

**Lymphoma and Other Malignancies**

Lymphoma and other malignancies have been observed in patients treated with RA in aphasidarc and other JAK inhibitors, including those receiving Rinvoq®. There have been reports of an increased risk of malignancies (including lymphomas) in patients treated with JAK inhibitors as compared to patients treated with TNF blockers.

**MALIGNANT NEOPLASMS**

A total of 2630 patients received at least 1 dose of Rinvoq® 15 mg, of whom 1860 were exposed for at least 6 months. Of these patients, 1.1% had a new malignant neoplasm attributable to treatment with Rinvoq®. The majority of these malignancies were lymphomas (1.1% of patients), and 1.1% of patients had a new malignancy attributable to Rinvoq®.

**OTHER INFECTIONS**

In a large, randomized, placebo-controlled clinical study of patients with moderate to severe RA treated with Rinvoq® 15 mg or placebo, 1.5% of patients treated with Rinvoq® had serious infections, compared to 0.5% of patients treated with placebo. Of these serious infections, 1 patient (0.03%) treated with Rinvoq® had a serious infection that led to death.

**DOSAGE AND ADMINISTRATION**

Rinvoq® is available in 15 mg and 30 mg extended-release tablets.

**ADVERSE REACTIONS**

**Nausea**

The most common adverse reactions reported with Rinvoq® were nausea (53%), headache (36%), abdominal pain (21%), and diarrhea (20%). Nausea was generally mild to moderate in severity and usually occurred within the first few weeks of initiation of Rinvoq® therapy.

**Viral Infections**

In a large, randomized, placebo-controlled trial of patients with moderate to severe RA treated with Rinvoq® 15 mg or placebo, 1.5% of patients treated with Rinvoq® had serious infections, compared to 0.5% of patients treated with placebo. Of these serious infections, 1 patient (0.03%) treated with Rinvoq® had a serious infection that led to death.

**Hypersensitivity Reactions**

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported in patients receiving Rinvoq®. Rinvoq® should be discontinued in patients who develop a hypersensitivity reaction, including anaphylaxis, and the use of antihistamines and corticosteroids may be indicated.

**Hematology**

Neutropenia is a common adverse reaction associated with Rinvoq® therapy. Neutropenia was reported in 4.3% of patients treated with placebo and 15.7% of patients treated with Rinvoq® 15 mg. The incidence of neutropenia was higher in patients with hemoglobin levels less than 8 g/dL at baseline.

**Hyperlipidemia**

Hyperlipidemia is a common adverse reaction associated with Rinvoq® therapy. Hyperlipidemia was reported in 4.3% of patients treated with placebo and 15.7% of patients treated with Rinvoq® 15 mg. The incidence of hyperlipidemia was higher in patients with hemoglobin levels less than 8 g/dL at baseline.

**Cardiac Thrombosis**

Cardiac thrombosis is a rare but serious adverse reaction associated with Rinvoq® therapy. Cardiac thrombosis was reported in 0.01% of patients treated with placebo and 0.05% of patients treated with Rinvoq® 15 mg. The incidence of cardiac thrombosis was higher in patients with hemoglobin levels less than 8 g/dL at baseline.

**Drug Interactions**

Rinvoq® can interact with other medications, including DMARDs, disease-modifying antirheumatic drugs, and immunosuppressants. Patients should be monitored for changes in lab values and have any needed adjustments made to their medication regimen.

**Food Interactions**

Rinvoq® is not affected by food intake and can be taken with or without food.

**Overdosage**

There is no specific treatment for overdose with Rinvoq®. Patients should be managed according to standard supportive care principles.

**PATIENT FOCUS**

Rinvoq® is available in 15 mg and 30 mg extended-release tablets. Rinvoq® should be taken once daily with or without food. Rinvoq® is associated with nausea, which can be managed by taking the medication with food or using anti-nausea medications.

**ADDITIONAL INFORMATION**

Rinvoq® is a small-molecule JAK inhibitor that is approved for the treatment of adults with mildly to moderately active RA, psoriatic arthritis, and ulcerative colitis. Rinvoq® is available in 15 mg and 30 mg extended-release tablets.

**PHARMACOLOGICAL ACTIONS**

Rinvoq® is a selective inhibitor of JAK1, which is involved in the signaling pathways that regulate the production of pro-inflammatory cytokines. Rinvoq® inhibits the release of these cytokines, thereby reducing inflammation and symptoms of RA, psoriatic arthritis, and ulcerative colitis.

**PHARMACOKINETICS**

Rinvoq® is rapidly absorbed after oral administration, with peak plasma concentrations achieved within 1-2 hours. Rinvoq® has a long plasma half-life, allowing once-daily dosing.

**CLINICAL TRIALS**

Rinvoq® has been studied in a variety of clinical trials. In a large, randomized, placebo-controlled trial of patients with RA, Rinvoq® significantly reduced the number of patients with new or active joint destruction compared to placebo. Rinvoq® was well tolerated, with a safety profile similar to placebo.

**REFERENCES**


Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as ritonavir, dexamethasone, dexamethasone, efavirenz, zidovudine, ritonavir, dexamethasone, efavirenz, zidovudine, or ritonavir-boosted atazanavir). In clinical studies, the median ratios of AUC and Cmax of upadacitinib from RINVOQ alone compared to co-administration with strong CYP3A4 inducers were 1.3 and 1.4, respectively. Therefore, when RINVOQ is co-administered with strong CYP3A4 inducers, monitor patients closely for evidence of reduced exposure to upadacitinib.

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as clarithromycin or azithromycin). In clinical studies, the median ratios of AUC and Cmax of upadacitinib from RINVOQ alone compared to co-administration with strong CYP3A4 inhibitors were 1.5 and 1.4, respectively. Therefore, when RINVOQ is co-administered with strong CYP3A4 inhibitors, monitor patients closely for evidence of increased exposure to upadacitinib.

Use with caution:
- Pregnancy:
  - Use RINVOQ during pregnancy only if the potential benefit justifies the potential risk to the fetus.
  - Women should not breastfeed during treatment with RINVOQ and for 6 days after the last dose of RINVOQ.
  - Advise women of reproductive potential to use effective contraception while receiving RINVOQ.
  - Advise women to avoid pregnancy at least 1 month before starting RINVOQ.

- Lactation:
  - Do not breastfeed during treatment with RINVOQ and for 6 days after the last dose of RINVOQ.
  - Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose of RINVOQ.

- Malignancies
  - Advise patients to report any new or worsening symptoms suggestive of malignancy to a healthcare provider.

Warning for infections
- Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of infection.

Use in specific populations
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Legal Issues Due To My Physician Extenders

L E G A L  E A G L E with David J. Goldberg, MD, JD

DR M HAS PRACTICED dermatology for 25 years. During that time, he has hired and fired secretaries and licensed medical assistants. He has never hired licensed physician assistants and nurses. His 3 most devoted and loyal employees have worked with him for more than 2 decades.

All 3 began their work with Dr M during high school as part-time secretaries paid minimum wage. After completing high school, they became full-time employees, and their tasks included answering the phone and scheduling patient appointments. These employees loved their jobs and never sought further schooling of any kind.

Over the course of 20 years, these employees became familiar with every aspect of Dr M’s dermatology practice. Due to so much clinical staff turnover, Dr M began asking these 3 women to play the role of medical assistants. At first they took dermatologic histories from patients, but after so many years of working in Dr M’s practice, all 3 “medical technicians” became very facile at acne surgery, small biopsies, simple suturing, and even some cosmetic procedures.

Dr M is convinced that these trained workers are more reliable and perform better quality work than any licensed medical personnel ever previously employed in his office. He is quick to tell his peers about the quality of their work and the fact that no medical malpractice litigation has ever ensued because of their labors.

Unfortunately, all 3 employees are served legal papers for practicing medicine without a license. In addition, Dr M is accused of aiding and abetting the practice of medicine without a license. Such a crime is a felony in his state and could force Dr M to lose his medical license.

Dr M is incensed and seeks legal advice. He doesn’t see how his actions could be considered a crime.

Aiding and abetting a crime means to assist the perpetrator of a crime. A person aids and abets the commission of a crime when he or she (1) with the knowledge of the unlawful purpose of the perpetrator, (2) and with the intent or purpose of committing, facilitating, or encouraging commission of the crime, (3) by act or advice, aids, promotes, encourages, or instigates the commission of a crime.

An aider and abettor is one who is present at the crime scene and by word or deed gives encouragement to the perpetrator of the crime or by conduct makes clear that he or she is ready to assist the perpetrator when such assistance is needed. To aid and abet another to commit a crime, one must associate with the venture, act with the knowledge that an offense is to be committed, and share in the criminal intent of the perpetrator of the crime. It should be noted that a person may aid and abet without actively participating in an overt act.

In Politi v State Medical Board, the record showed that Barry J. Politi, MD, specifically limited the conduct of his assistant who was not properly registered as a physician’s assistant but was a registered nurse while working for Politi. There was no evidence that the assistant made any independent medical judgment or performed any medical procedures. The assistant’s conduct never exceeded the scope of practice for a nurse. Thus, the court ruled that the Ohio State Medical Board improperly imposed a penalty on Politi for assisting and abetting a nurse in the unauthorized practice of medicine.

In Siddiqui v Department of Professional Regulation, the court held that the purpose of the Illinois Medical Practice Act of 1987 is to protect the public health and welfare from those not qualified to practice medicine. Jawed Siddiqui, MD, was assisted by a trained and licensed pharmacist’s assistant. Siddiqui was charged with allowing the assistant to use his medical license as well as aiding the assistant in the unlicensed practice of medicine in violation of the Illinois Medical Practice Act. Specific acts performed by the assistant included the removal of sutures, the administration of injections, the diagnosis of diseases in patients, and the prescription of medications by signing Siddiqui’s name on prescription blanks.

Siddiqui argued that not every act performed by a physician constituted the practice of medicine. The court conceded that duties such as changing bandages, administering injections, and drawing blood are often performed by nonphysicians. However, the court found that diagnosing disease and making final decisions about the treatment of patients by prescribing medications, even by reissuing prior prescriptions, crossed the line into the practice of medicine. The fact that licensed professionals other than physicians could legally perform certain medical procedures under the supervision of a physician did not exempt the performance of those same procedures by an unsupervised and unlicensed individual from the scope of the Medical Practice Act.

Dr M’s assistants may be more valuable than any licensed health care professionals he has ever hired. Nevertheless, they are not licensed health care professionals. He may be found guilty of aiding and abetting a crime.

David J. Goldberg, MD, JD, is medical director of Skin Laser and Surgery Specialists of New York and New Jersey; director of cosmetic dermatology and clinical research at Schweiger Dermatology Group in New York, New York; and clinical professor of dermatology and past director of Mohs Surgery and Laser Research at the Icahn School of Medicine at Mount Sinai in New York, New York.
**Peptides and Skin Care**

**Q** What is the function of peptides in skin care?

Peptides are composed of various numbers of amino acids. A dipeptide consists of 2 amino acids, a tripeptide consists of 3 amino acids, and a tetrapeptide consists of 4 amino acids. Not only is the number of amino acids important, but also the order in which the amino acids are arranged. For example, glycyl-histidyl-lysine is thought to stimulate collagen synthesis in fibroblasts, whereas glycyl-lysyl-histidyl is thought to stimulate lipolysis in adipocytes. Nevertheless, the function of a peptide in skin care is to transmit a biochemical message from one body area to another body area, providing for communication of a physiologic change.

**Q** What are the most commonly used antioxidant peptides?

The 2 most frequently used antioxidant peptides in skin care are glutathione (β-glutamyl-cysteinyl-glycine) and carnosine (γ-alamyl-L-histidine). Glutathione is a tripeptide abbreviated GSH. Because the level of glutathione decreases with age, the topical use of the antioxidant peptide is thought to possess aning properties, despite limited evidence of clinical benefit topically.

Carnosine is a well-known scavenger of reactive oxygen species in the cell membrane, preventing the oxidation of free fatty acids. It can also inhibit the formation of skin advanced glycation end products by preventing the nonenzymatic binding of sugars to proteins. Over time, carnosine is degraded to β-alanine and histamine. β-Alanine is thought to stimulate the biosynthesis of nucleic acids and collagen. Thus, both the peptide and its breakdown products are thought to be biologically active.

**Q** What are tissue repair peptides?

The idea that a peptide applied to either a wound bed or intact skin could stimulate collagen production is compelling. These fragmented macromolecules are known as matrikines. Matrikines recycle breakdown fragments of larger molecules, such as collagen, to trigger repair activity. For example, the most widely used matrinike peptide in skin care is the pentapeptide Pal-KTTKS, composed of palmitic acid, lysine, threonine, threonine, and serine, also known as palmitoyl pentapeptide-4. This is the name that will be found on the ingredient disclosure list when this peptide is used. This pentapeptide is the shortest type 1 procollagen fragment capable of stimulating fibroblast collagen synthesis in a petri dish. It was discovered by serially cleaving collagen and putting the fragments on fibroblast cell cultures to see which cultures produced more collagen.

It can be challenging to fully understand the true benefit of tissue repair peptides and peptides in general. Due to expense, peptides are used in a concentration of parts per million. It is thought that because they are modifying a biologic process, a small amount will produce sufficient results to see appearance improvement. However, it is not possible to apply pure peptide to the skin in such low concentrations. The peptide must be delivered in some type of vehicle, usually a moisturizer, to spread the active ingredient over the skin surface. This means that it can be hard to separate the moisturizing vehicle benefit from the peptide benefit. Vehicle controlled studies are the best way to determine the added benefit of the peptide, but they are seldomly performed.

**COSMETIC CONUNDRUMS**

with Zoe Diana Draelos, MD

**What are the most frequently used antioxidant peptides?**

The 2 most frequently used antioxidant peptides in skin care are glutathione (β-glutamyl-cysteinyl-glycine) and carnosine (γ-alamyl-L-histidine). Glutathione is a tripeptide abbreviated GSH. Because the level of glutathione decreases with age, the topical use of the antioxidant peptide is thought to possess aning properties, despite limited evidence of clinical benefit topically.

**Pigmentary Disorders**

**New Treatment Targets Nonsegmental Vitiligo**

Lois Levine, MA, Associate Editorial Director

“I OFTEN FEEL that I’m losing the very thing that identifies me as a Black woman” is just one of the things that patients say when talking about vitiligo, explained Pearl Grimes, MD, during her presentation at the recent Skin of Color Update 2022 meeting.1 held September 9 to 11 in New York City. “Vitiligo is a major social stigma, and everyone’s reason for seeking treatment is different. That’s why it was so exciting for me to see a first-time-ever FDA-approved drug for repigmentation of vitiligo. Everything else up to this date that we used was off-label.”

Ruxolitinib cream 1% (Oprelura) was approved in July 2022 for the treatment of nonsegmental vitiligo in patients 12 years and older.2 Grimes, director of The Grimes Center of Medical and Aesthetic Dermatology and of the Vitiligo & Pigmentation Institute of Southern California, both in Los Angeles, started prescribing it to her patients almost immediately.

“Vitiligo is a classic autoimmune disease,” she noted. Risk factors for vitiligo include a genetic susceptibility (25%-50% of individuals with vitiligo have a relative with the disorder), sunburn, physical skin trauma, psychological stress, and other factors. Because vitiligo can also be connected to other autoimmune conditions (thyroid, alopecia areata), Grimes urged practitioners to do baseline labs before considering treatment options.

Vitiligo affects approximately 2 to 3 million adults in the United States, with 30% often developing the condition prior to age 20 years, noted Grimes—a difficult psychosocial burden for a young adult to carry. The disease affects individuals of all ethnicities, skin types, and gender. For segmental vitiligo, Grimes noted that the loss of pigmentation often burns out in a year. “This is the most predictable and curable type of vitiligo,” she said, whereas nonsegmental vitiligo (the majority of cases) is more challenging, progresses slowly, and has a more unpredictable course.

Before the approval of ruxolitinib, a variety of off-label treatments were used to treat nonsegmental vitiligo, including topical and oral corticosteroids, topical calcineurin inhibitors, and even surgical therapy. “There was an unmet need for a treatment directly targeting this disease,” Grimes said.

Ruxolitinib is a key driver for depigmentation by targeting and inhibiting the JAK/STAT pathway to reduce inflammation, Grimes explained. Reducing this inflammation creates a more stable environment that promotes production of melanocytes and repigmentation. Although ruxolitinib can certainly be called a game changer for treating vitiligo, Grimes emphasized that “monitoring is key.” She noted that adverse effects include acne, pruritis, headache, and urinary tract infection and that safety considerations include watching for thrombocytopoenia, anemia, neutropenia, and lipid elevations.

“You must always look at the data from a risk-benefit ratio. Screen patients at baseline and throughout treatment with ruxolitinib,”3 Grimes concluded, adding that “the efficacy is significantly greater than the [adverse] effects [Ruxolitinib] creates a favorable environment for the regrowth of pigment cells.”

Reference


Estate Planning Essentials: What Dermatologists Should Know

With David Mandell, JD, MBA; and Carole Foox, CPA

THE TERM ESTATE PLANNING is commonly known to dermatologists, along with most individuals, as the type of planning one does in contemplation of death—creating wills, trusts, and other documents to handle issues after one is gone. Although that is part of the discipline, it is not all. Rather, proper estate planning should encompass several tactics that can have significant impact during one’s life, from annual gifts to planning for the possibility of being legally incapacitated.

In fact, estate planning can be thought of as the following 3 distinct planning areas:

- Incapacitation Planning deals with decision-making regarding legal, financial, and medical issues if one is unable to make decisions for oneself.
- Estate Distribution Planning concerns what happens to assets upon death.
- Transfer Tax Planning addresses and plans for the various gift, estate, and other taxes that may be triggered under state and federal laws when transferring wealth during life or at death.

In this article, we will provide an overview of incapacitation planning and estate distribution planning, including the recommended documents for each.

Incapacitation Planning
Planning for one’s own incapacitation (ie, what happens if you are not able to make decisions for yourself) is never pleasant but always important.

As an example, what happens if you are hospitalized and cannot express your wishes regarding decisions that need to be made about your medical care? Many physicians assume that their family members would automatically be able to make decisions in this scenario. However, rules vary greatly from state to state. In some cases, decisions are left up to the health care providers and institutions in charge of your care. Also consider what may happen if such decisions can be made by your family members, but they do not all agree on the best course of action.

You should have several key documents in place. The exact names and requirements are controlled by state law and will vary. These documents include the following:

- **Living will.** This is a written record of the type of medical care you would want in specific circumstances.
- **Health care proxy.** This document names someone you trust as your proxy, or agent, to express your wishes and make health care decisions for you if you are unable to speak for yourself.
- **Advance directive.** This term often refers to a combination of the living will and health care proxy documents.
- **Power of attorney.** This document names someone you trust as your agent to make property, financial, and other legal decisions on your behalf.

Estate Distribution Planning
If you die without a will, then your property will pass under the scheme that your state legislature has written for its citizens. This is what is known as dying “intestate.”

There are various negative consequences of dying intestate. Although the precise rules vary among the 50 states, the laws are typically very rigid and formulaic. Usually, your nearest relatives get a piece of your property, but no one else does— not friends, cousins, charities, or anyone else. Furthermore, no one gets more than the state-allotted share, even if that seems unfair. Often, this ends up hurting the surviving spouse if there is one. In this all-too-common scenario, the decedent’s grown children may get some of the money meant for the surviving spouse, even if it means the surviving spouse then has too little to live on. In larger estates, this could have the very impractical effect of creating an estate tax payable when the first spouse dies if the children’s intestate share of the estate exceeds the federal or state exemption amount. Moreover, intestacy may lead to expensive and lengthy court battles by family members contesting the division of assets.

Perhaps the most upsetting thing about intestacy is what occurs if one has minor children: If both parents die intestate, the courts will decide who becomes the legal guardian of the children. Furthermore, any minor children will receive their share of the estate when they turn age 18 years, rather than at some more appropriate later age that one can specify with proper planning.

Living Trusts and Pour-Over Wills
Although estate planning documentation is completely state dependent, we can say that in every state, having a will is better than not having a will. However, in many states, with a will alone, your entire estate will be stuck in the probate process. Probate is the court-controlled public process by which the state administers your will.

In most states, knowledgeable estate planning advisors recommend combining a living trust with a short will called a “pour-over will” because this combination ensures that much of an estate will avoid probate. Depending on the state, probate can be time-consuming, public, and very costly. In many states, the goal is to avoid the process as much as possible.

The Living Trust: A Foundational Estate Planning Document
Living trust (or “family trust”) is a common name given to a revocable trust (which, unsurprisingly, is revocable, meaning you can revoke it or amend it anytime during your life).

Regardless of its marketing name, the living trust is a revocable trust that provides direction for the use of your assets both while you are alive and at the time of your death. During your life, the assets transferred to the trust are managed and controlled by you, as the trustee, just as if you owned them in your own name. When you die, these trust assets pass to whomever you designated in the trust, automatically, outside the probate process. Other benefits of the living trust include the following:

- prevention of court control of assets if you become incapacitated;
- protection of beneficiaries with special needs; and
- the ability to nominate guardians to take care of your children if you are incapacitated (but still alive) or when you die.
Inflation Reduction Act: The Impact on Physicians

Michael Joyce, CFA, CFP — From our sister publication, Medical Economics’

AFTER A YEAR of deadlocked negotiations and a great deal of waiting and wondering, Congress has passed the Inflation Reduction Act of 2022 (IRA). With President Joe Biden having recently signed the bill, you may be wondering how the IRA will impact the lives and wallets of physicians. Some effects will be indirect, some will be felt directly, and other elements of the IRA will not be felt at all.

Let’s look at the tax planning and financial planning implications of the legislation for doctors and medical system executives.

Corporate Minimum Tax
One of the most significant features of the IRA is the new corporate minimum tax of 15% for businesses with revenues greater than $1 billion annually.

Doctors, medical system executives—and most investors for that matter—may very well be indirectly impacted by the corporate minimum tax because this new tax expenditure has the potential to reduce corporate dividends and, therefore, the retirement savings of investors.

More directly, the 15% corporate minimum tax is likely to impact employees of businesses with more than $1 billion a year in revenue—possibly resulting in slower wage growth (smaller raises and bonuses, etc.) It may also slow hiring. So when it comes to physicians, those in private practices would not feel these effects directly because their practices’ revenues would not be $1 billion, but those who work for large hospital systems could very well be affected. It’s possible, of course, that physician groups could negotiate not having salary/bonus structures reduced by the new corporate minimum tax, but the potential is certainly there.

Tax Credits for Electric Vehicles and Home Upgrades
You have likely read about the extension of tax credits on electric cars included in the IRA ($7500 tax credit for new electric vehicles and $4000 for a used one). But eligibility for these tax credits is determined by income level. Physicians, medical system executives, and others with annual incomes more than $150,000 individually or $300,000 jointly will not be eligible for the electric car tax credits. And the tax credits enacted for home upgrades (ie, solar panels, better insulation, and heat pumps) have similar income limits.

Carried Interest Loophole
One piece of the IRA that has been widely reported on that will not affect doctors and medical system executives is what some headlines have misleadingly referred to as the “carried interest loophole for wealthy people.” The loophole was preserved in the IRA after a great deal of back and forth. Although it is accurate that carried interest will continue to receive preferential tax treatment and that those who earn carried interest are generally wealthy people, closing the loophole would have only applied to those who manage investments and earn a performance fee, such as hedge fund managers, private equity fund managers, and real estate fund managers. So neither physicians nor medical system executives (or most other wealthy individuals) would have benefited from the preservation of the carried interest loophole.

Additional Elements of the IRA
One element of the IRA that has been widely publicized is the $2000 cap on Medicare beneficiaries’ annual out-of-pocket drug expenses. Those with private insurance have no such cap. The new legislation extends Affordable Care Act health insurance premium assistance for 3 years, through 2025. Had the Affordable Care Act premium assistance not been extended, the costs would have escalated and some patients may have given up insurance coverage altogether. As a result, they may have canceled or postponed medical appointments and procedures.

Internal Revenue Service Enforcement
In addition, the IRA will increase Internal Revenue Service enforcement with the hiring more agents to conduct audits of higher-wage earners. This could impact physicians if for no other reason than the hassle factor. I am always skeptical that more audits will correlate to the increases in government revenue projected by such enforcement. It would be better if the Internal Revenue Service hired more agents to answer their phones or open correspondence, including returns that have been filed.

Final Thoughts
Physicians in private practice will experience very little upside or downside due to the IRA. Those working for larger health systems are at greater risk of being impacted negatively by the 15% corporate minimum tax. And both groups—those in private practice and those in larger health systems—should be careful to dot their i’s and cross their t’s when filing their tax returns. Employing a trusted certified public accountant to file next year’s 2022 tax returns would probably be a smart move.

Michael Joyce, CFA, CFP, is founder and president of Agili, a registered investment adviser and fiduciary in Richmond, Virginia, and Bethlehem, Pennsylvania. He is responsible for overall investment strategy, management of investment portfolios, and financial planning services. He can be reached at MJoyce@AgiliPersonalCFO.com.
OPZELURA was studied in 2 identically designed, double-blind, randomized, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2). The 2 studies included 1249 adult and adolescent patients ≥12 years of age with an affected BSA of 3%-20% and an IGA score of 2 or 3 on a severity scale of 0-4. Patients were randomized to monotherapy with OPZELURA, ruxolitinib cream 0.75%, or vehicle twice daily for 8 weeks.1,2

*With a ≥2-grade improvement from baseline.1
†In TRuE-AD1 and TRuE-AD2, respectively.4,5
‡≥4-point improvement in NRS among patients with a score of ≥4 at baseline.6

BSA=body surface area; IGA=investigator’s Global Assessment; JAK=Janus kinase; NRS=numeric rating scale.
INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adult and pediatric 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 cryptococcosis and pneumocystosis.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib.

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.

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.

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on following pages.
IMPORTANT SAFETY INFORMATION for OPZELURA™ (ruxolitinib) cream 1.5% (continued)

MORTALITY
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

MALIGNANCIES
Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. 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 when on treatment, and patients who are current or past smokers.

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. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke.

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 they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS
Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately.

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
In atopic dermatitis, 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 is 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.

Lactation
Advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

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

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 cryptococcosis, and pneumocystis.  • Bacterial, viral, including herpes zoster, 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
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality was observed when compared with TNF blockers. A higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor [see Warnings and Precautions].

MALIGNANCIES
Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk [see Warnings and Precautions].

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OPZELURA in patients who have experienced a myocardial infarction or stroke [see Warnings and Precautions].

THROMBOSIS
Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately [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 tuberculosis 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.

Thrombosis: 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 or active TB infection prior to administration of OPZELURA. Do not resume 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: In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality was observed when compared with TNF blockers. A higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. 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 JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies. 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 when on treatment, 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 skin examinations during OPZELURA treatment and follow treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

Major Adverse Cardiovascular Events (MACE): In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, non-fatal myocardial infarction, MI, and non-fatal stroke) was observed with the JAK inhibitor compared to those treated with TNF blockers. 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 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 they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

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 (TRU-EAD1 and TRU-EAD2), 499 adult and pediatric 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) 152 (21%) vs 83 (33%), Naegleria fowleri 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Essonophil 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 Rhinorhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in TRU-EAD1 and TRU-EAD2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, uteris externa, Staphylococcal infection, and acneform 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 is 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 dose of 15 mg/kg/day 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% atopic dermatitis-affected body surface area is used for calculation of multiples of human exposure). In rabbits, lower fetal weights of approximately 6% 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 treated 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 5-6 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: Atopic Dermatitis: The safety and effectiveness of OPZELURA for the topical treatment of mild-to-moderate atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRU-EAD1 and TRU-EAD2, which included 92 pediatric subjects aged 12 to 17 years with mild-to-moderate atopic dermatitis. 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 with atopic dermatitis 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 (9%) were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between subjects less than 65 years and subjects 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 [see Warnings and Precautions].

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Advise 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. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen [see Warnings and Precautions].

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatality myocardial infarction, non-fatality 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 [see Warnings and Precautions].

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

Thrombocytopenia, Anemia, and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Inform 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 one 60 gram tube per week or one 100 gram tube per 2 weeks [see Dosage and Administration].

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 about four weeks after the last dose [see Use in Specific Populations].

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

OPZELURA is a trademark of Incyte. All rights reserved. U.S. Patent Nos. 7598257; 8413536; 6722693; 8822481; 9079912; 9974790; 10063930; 10610530; 10756843; 10869870; 12119624 © 2022 Incyte Corporation. All rights reserved. Issued: July 2022 PRL-0PZ-00023
A Look at the Rise in Adult Acne in Women

Understanding the main causes and staying current on recommendations and treatments will help reduce patient rates of the condition.

Sandra Fyfe, Staff Correspondent

Adult acne in women has increased 10% worldwide over the past 10 years, according to a 2022 review of adult acne conducted by Brigitte Dreno, MD, PhD, head of the Department of Dermatology at Nantes University Hospital in France, and colleagues. The review was published in the International Journal of Dermatology.1

“Adult acne has serious consequences, including psychological impact, low self-esteem, social isolation, and depression,” the authors wrote. The condition affects more than 640 million people across the globe, with the biggest risk factor being heredity.1 However, there are factors under patient control, such as diet, that can reduce acne risk.

Treatment approaches vary by gender, and newer treatments are in the pipeline, including skin microbiome modulation, which would be helpful in reducing antibiotic use and preventing microbial resistance.1

Anais Aurora Badia, MD, DO, an adult and pediatric dermatologist and founder of the Florida Skin Center, now part of Advanced Dermatology and Cosmetic Surgery in Fort Myers and Lehigh Acres, Florida, spoke with Dermatology Times on the increasing rates of adult acne and how to treat it.

Factors Contributing to Adult Acne

Badia said that adult acne and adolescent acne share similar causes and that acne is mostly caused by sebum production, inflammation, and bacteria. “Stress, hormones and diet can increase inflammation,” she said. “When our stress levels rise, we produce higher levels of acne-causing androgens, which can stimulate oil glands and hair follicles that contribute to acne.”

In addition to stress—which has been considerably higher these past few years due to the pandemic—Badia said that masks worn to protect against COVID-19 increased acne rates because they trap dirt and bacteria on the skin, which contributes to an increase of the acne-causing bacteria Propionibacterium acnes.

Badia also noted gender differences in acne prevalence. “Increased hormone levels contribute to acne in both men and women. However, the types of hormones causing acne are different for each,” she explained. “Women tend to see more fluctuations in hormones than men due to medications, menstrual cycles, and menopause,” which is why women get more acne than men.5

Diet also plays a role in developing acne. “Some small studies have shown a link between dairy con-

sumption causing an increased risk for acne,” Badia said. “Other studies have linked high glycemic index foods to acne [because] these foods spike our blood sugars rapidly, causing inflammation, which in turn leads to an increase in acne.”

The review by Dreno and colleagues also found that milk, sugar, sugary drinks, and fatty foods were associated with acne in adults.1

Badia added that skin and hair products can also cause acne. She said that dermatologists should advise patients to read labels and look for products that say noncomedogenic or oil free.

“It is also important they be advised to use products with physical sunscreens, such as zinc oxide or titanium dioxide,” she said.

Treatments

Badia noted that each patient should be treated based on their individual needs and concerns. The adult acne review by Dreno and colleagues contained a summary of the 2018 international consensus treatment recommendations from the Global Alliance to Improve Outcomes in Acne Group. The recommendations are as follows:2

1. Factors Contributing to Adult Acne
2. Treatment

Adult acne in women has increased 10% worldwide over the past 10 years.
Recommendation 1 Retinoids play an essential role in acne treatment, with a topical retinoid and benzoyl peroxide as first-line treatment for inflammatory acne and/or comedonal acne.

Recommendation 2 Systemic and topical antibiotics should be avoided as monotherapy.

Recommendation 3 Very severe (cystic and conglobata) acne should be treated with oral isotretinoin.

Recommendation 4 Patients should take oral isotretinoin until their acne clears. Total cumulative dosage to keep acne in remission needs more studies.

Recommendation 5 Use low-dose oral isotretinoin to minimize acne flares.

Recommendation 6 Maintenance therapy with a topical retinoid combined or not with benzoyl peroxide should be used for most patients. Avoid topical antibiotics for maintenance therapy.

Recommendation 7 Pregnant women and patients with acne and postinflammatory hyperpigmentation should be prescribed azelaic acid cream 20% or gel 15%.

Recommendation 8 Do not use devices (laser, intense pulsed light, photodynamic therapy) as first-line treatments for inflammatory acne.

Recommendation 9 In a small number of women 25 years and older, only the lower face is affected by acne. Topical retinoids with or without benzoyl peroxide should be used.

Recommendation 10 Starting treatment early minimizes the risk of scarring.

Newer Novel Treatments

Badia noted that acne therapies have come a long way. “With concerns about antibacterial resistance on the rise, a new topical minocycline [Amzeeq] is the first of its kind to deliver antibiotic therapy with minimal systemic absorption,” she noted. “Another novel medication for acne is clascoterone cream 1% [Winlevi]. This medication is an antagonist of dihydrotestosterone and prohibits the production of sebum.” She explained that clascoterone is similar in structure to spironolactone but has minimal systemic antiandrogen effects and is safe for both men and women.

She added that topical retinoids continue to be “the gold standard in acne treatment” and that “many new formulations...have come out recently with age indications as young as 9 years old.”

Acne Prevention: Patient Guidance

Badia recommended advising patients of the following:

- Protect their skin by using a daily SPF with zinc oxide and by not actively tanning.
- Clean their faces daily with a gentle cleanser.
- Avoid products that contain alcohol, harsh exfoliants, and astringents that can irritate the skin and make acne worse.
- Avoid popping or picking acne lesions because this could lead to more acne and scarring.

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Overview of Prurigo Nodularis for Practicing Dermatology Clinicians

It is crucial to better understand, diagnose, and manage this skin condition associated with significant quality-of-life impairment.

Xindi Chen; Viviane Liao; and Bernard A. Cohen, MD

Prurigo nodularis (PN) is a chronic inflammatory skin condition characterized by intense pruritis, taking the form of firm, hyperplastic, intensely itchy nodules often found on extensor surfaces of the limbs and trunk. Although exact pathogenesis is still unclear, PN has been shown to be associated with neural and immune dysregulation mediated by inflammatory cytokines and neuropeptides, leading to the condition’s persistent, severe itch. In part due to lack of understanding of pathophysiology, there are no FDA-approved treatments. Given the condition’s detrimental impact on quality of life, it is critical to better diagnose, manage, and understand PN, as well as the itch and pain associated with significant morbidity.

Variation in Presentation
A patient with PN will typically present with firm nodules symmetrically distributed in groups on extensor surfaces of the arms, legs, and trunk. Notably, lesions typically spare the middle upper back in what is termed the “butterfly” sign. Nodule appearance can vary—typically measuring a few millimeters to 2 cm, ranging from flesh-colored to pink to brown to black, and numbering a few to hundreds.1 Skin color may also affect presentation; for Black patients, for example, PN nodules may be firmer, larger, and darker.

Repeated itching and mechanical scratching frequently leads to thickening, crusting, and excoriation of the nodules over time, which can lead to scarring as nodules heal.1 Most patients report severe itching accompanied by sensations of pain, stinging, and burning in both nodular and internodular skin.1 The itch, pain, and stress can significantly impact quality of life and health care utilization. Aggarwal et al found that patients with PN had mean scores of 16.4, 11.6 and 16.8 on the Dermatology Life Quality Index, Pittsburgh Sleep Quality Index, and 5-Dimensions Itch scale, respectively, as well as a high medical-appointment burden, with 36.3% of 231 surveyed patients reporting 10 or more doctor visits in the past year.9

Epidemiology
PN is relatively rare, with an estimated prevalence of 22 to 72 per 100,000 adults.4,5 These estimates, however, may be conservative due to inconsistency in PN coding. Additionally, more work needs done to understand prevalence in the pediatric population.4 In the adult population, PN commonly affects middle-aged patients in the fifth and sixth decades of life, with an epidemiologic study of 7095 adult patients suggesting that the diagnosis is more common in women than men (53.1% vs. 46.9%).6 Patients with skin of color are also at increased risk, as shown by both single-institution and national database research. Compared with White patients, African American patients are roughly 3.4 times more likely to have PN.7 There is also increased burden for inpatient stays for African American, Asian, and Hispanic patients with PN.8 Factors such as inadequately treated atopic dermatitis and barriers in health care access may increase the risk of concomitant PN in patients of color.

Studies comparing PN with other inflammatory skin conditions have also shown a higher burden of systemic comorbidities with PN. Given the complex immune dysregulation associated with PN, it may come as little surprise that PN is associated with other dermatologic diseases, most commonly atopic dermatitis as well as psoriasis, neurotic excoriations, keratoacanthomas, and bullous pemphigoid. In addition to dermatologic conditions, PN is also linked to multiorgan systemic diseases spanning infection, metabolic dysfunction, and malignancy. Notably, patients with PN have 2.68 higher odds of HIV infection and 2 to 5 times increased odds of non-Hodgkin lymphoma when compared with controls.4

Other common copresenting conditions include celiac disease, thyroid disease, diabetes, multiple myeloma, primary cutaneous lymphoma, and end-stage renal disease. Patients with PN also have increased rates of mood and anxiety disorders vs age- and sex-matched controls and other patients with atopic dermatitis and psoriasis.4 There are also increased odds of self-harm, eating disorders, schizophrenia, and other mental health conditions.5,6

Although more research is needed to clarify causal relationship between PN and copresenting conditions, the diverse range of comorbidities may promote the itch-scratch cycle and PN worsening.

Diagnosis
PN is a primarily clinical diagnosis based on history and physical examination. Key findings include the presence of symmetrical, firm, nodular lesions on the extensor limbs and trunk of the body that spare the middle upper back (butterfly sign), pruritus lasting longer than 6 weeks, and history of repeated scratching of lesions. Other conditions that may present similarly and trigger PN include insect bites, scabies surreptitius (mistaken for other dermatologic diagnoses),
epidermolysis bullosa, hypertrophic lichen planus, include pemphigoid nodularis, actinic prurigo, differential diagnoses that present less commonly absorption.11 Intralesional injections of corticosteroids, aiming to reduce inflammation, often betamethasone valerate 0.1%, are required to achieve control of the condition.3 Treatment
manifestations in adults are better understood, PN may be used for patients refractory to treatment with topical treatments because it has proved to be effective in many studies and has minimal adverse effects. Both psoralen plus UV-A (PUVA) and narrowband UV-B are used with similar success, although a trial of 22 patients with PN showed that using both PUVA and UV-B excimer light in combination reduces the number of PUVA sessions required to achieve complete or almost complete remission of PN.1 Systemic treatments are often required, as many patients with PN are refractory to topical treatments and phototherapy. Immunomodulators used for PN include oral cyclosporine and methotrexate, although they must be used carefully due to their adverse effect profiles and patients should be monitored throughout use.11 Neuromodulatory treatments include gabapentinoids, antidepressants, opioid receptor agonists/antagonists, neurokinin-1 receptor (NKIR) antagonists, and thalidomide. Gabapentinoids, such as gabapentin and pregabalain, target calcium signaling in rich. However, providers should be mindful of the risk of sedation in patients with higher doses of gabapentinoids and may need to slowly titrate treatment upward. Antidepressants, including paroxetine, duloxetine, amitriptyline, fluoxetine, and mirtazapine, also have reduced itch in small studies of patients with PN.9 Because dysregulation in activation of opioid receptors has been implicated in itch, the opioid receptor antagonists naltrxone and naloxone have been effective in case series in reducing itch and improving lesions.12 Oral nalbutphine ER (Hadu-vio), a mixed κ opioid receptor agonist/µ opioid receptor antagonist also shows promise in phase 2b/3 clinical trials.12 Aprepitant and sorapant are NKIR antagonists that target substance P, a peptide shown to be elevated in PN lesions. They have previously shown success in small studies but failed to show efficacy vs placebo in larger randomized controlled trials. Finally, thalidomide may be used for patients refractory to treatment but should be prescribed carefully due to its teratogenic and neurotoxic effects.13 Several novel therapies are in development for treatment of PN. Dupilumab, a biologic that targets the IL-4 receptor, is already approved by the FDA for atopic dermatitis and elicited clinically significant reduction in itch in 60% of patients with PN vs 18% of patients with PN treated with placebo.15 Nemolizumab, another biologic, targets the IL-31 receptor and also elicited significant reduction in itch in 56% of patients with PN vs 21% of patients with PN treated with placebo.16 Vaxarelimum, which targets monocost M receptor G, and barzoxel-limab, which targets the mast cell KIT receptor, are also promising biologics in phase 2 and phase 1 clinical trials for PN, respectively. Finally, abrocitinib is a JAK1 inhibitor that targets several inflammatory pathways and is in phase 2 clinical trials.17

Many of these systemic therapies are also in development for other primary dermatologic disorders such as atopic dermatitis and psoriasis, which may create opportunities for treatment synergy given the high degree of PN comorbidity. With further research, these treatment options hold great promise for providing more reliably effective treatments for patients with PN.1

References
Exploring the Relationship Between Psoriatic Arthritis and Psoriasis

Carrie Nagorka, Senior Editor

Patients with arthritis are often first diagnosed with psoriasis. In this excerpt from a Dermatology Times’ DermView video episode, 2 physicians explored the relationship between the skin and joint disorders, why the two are often related, and some of the medications that may bring relief for patients with both conditions.

Relationship Between Psoriatic Arthritis and Psoriasis

“About a third of our patients with psoriasis go on to psoriatic arthritis [PsA]. And we know there are certain risk factors that increase the likelihood that a patient is going to develop psoriatic arthritis. That includes factors such as nail disease, inverse psoriasis, scalp psoriasis, more severe psoriasis, obesity, and family history of psoriatic arthritis, specifically in a first- or second-degree relative,” said Joseph Merola MD, MMSc, vice chair of clinical trials and innovation in the Department of Dermatology, director of the Clinical Unit for Research Innovation and Trials, and director of the Center for Skin and Related Musculoskeletal Diseases at Brigham and Women’s Hospital and associate professor of dermatology and rheumatology at Harvard Medical. Although there may be a genetic risk factor, with overlapping risks between skin and joint disease, environmental factors can also trigger the immune response that becomes psoriasis and leads to psoriatic arthritis.

Mark Lebwohl, MD, dean of clinical therapeutics at the Kimberly and Eric J. Waldman Department of Dermatology at Icahn School of Medicine at Mount Sinai in New York, New York, noted that 70% of patients with arthritis are first diagnosed with psoriasis and that arthritis occurs before psoriasis 15% of the time. Plaque psoriasis is the predominant presenting form of psoriasis.

Lebwohl then explained the domains of the disease and the different preexisting conditions that dermatologists see in many patients before a diagnosis, including nail disease, scalp disease, or inverse and intertriginous psoriasis. “I would say close to 20% come in with guttate psoriasis. [Pustular psoriasis and erythrodermic psoriasis are exceedingly rare], but those are deadly ones. And of course, in plaque [psoriasis] we include inverse palm and sole psoriasis, [which is] less common than just plaque psoriasis.”

Somatic patients also show signs of other types of arthritis, including the following:
- Axial PsA, which involves sacroiliitis, the inflammation of 1 or more joints where the lower spine connects with the pelvis
- Dactylitis, which involves the global swelling of a finger or toe
- Enthesitis, which is inflammation at sites where the tendon or ligament connect to the bone

Treatment Options

The treatments for PsA also work for psoriasis. The physicians discussed a few widely used treatments such as TNF-α blockers, IL-17 blockers, and Janus kinase inhibitors. Several Janus kinase inhibitors were approved in 2022 for the treatment of psoriasis and PsA, and Lebwohl said they work well, despite some boxed warnings that come with the drugs. He added that doctor involvement is key. It is up to the physician to ask questions to help the patient pinpoint the source of pain or stiffness.

The physicians discussed the reasons a physician may choose one category of drug over another. They agree that TNF-α blockers are the best evidence to date that they prevent heart attacks. For patients who have preexisting heart conditions, a drug in that category would be the first line of defense.

Lebwohl explained this is important because of a marked increase in the risk of heart attacks in patients with psoriasis. If a patient has or had skin cancer, a TNF-α blocker would not likely be the first choice, because a side effect is an increased risk of squamous cells.

In addition, they mentioned that patients with PsA who are pregnant could benefit from certolizumab pegol (Cimzia), a drug that does not contaminate breast milk and therefore will not cross the placenta. Dermatologists often start women of childbearing years on certolizumab pegol for that reason.

The patient’s weight also factors into some treatment plans. “We know that one of the unique aspects of some of our infusion therapies, in particular infliximab (Remicade; Janssen Biotech, Inc), is that it is weight-based dosing.” Merola said. “It does offer—albeit off-label—dose flexibility around frequency dosing. IV [intravenous] dosing is...weight based but has flexibility around frequency. I can do it every 4 weeks, every 6 weeks. I can do 5 mg/kg. I can do 10 mg/kg.”

Merola noted that some of the highest efficacy in PsA was shown in findings from the GO-VIBRANT trial (NCT02181673) that examined intravenous golimumab (Simponi Aria).

The physicians also mentioned treatment options when a drug fails to yield positive results. Lebwohl and Merola described primary failure as the ineffectiveness of a drug; no history of a response. A secondary failure, they said, indicates a lack of response after an initial period of success. A practitioner may prescribe a new classification of drugs for a patient who experiences primary failure.

In a secondary failure, the doctor may have to increase the dosing or move to a new treatment plan. Merola said that one cause for secondary failure is due to the patients’ development of antibodies; they would then have to prescribe an additional medication to suppress their formation.

Both physicians agreed that the number of drugs available for PsA is always increasing, which means more access for doctors and patients. “We have robust data from studies that support that switching [medications] seems to be well tolerated, seems to continue efficacy for our patients with these disorders,” Merola said. However, patients often have negative expectations about what changing drugs means, which may lead to confusion, more calls to the office, or failure to take the drugs.

Merola and Lebwohl concluded by talking about the importance of regular screenings for PsA or psoriasis patients. Merola suggested a frequency of every 6 months to record new or worsening symptoms and to keep track of disease progression.

Transcript edited for clarity and conciseness.

Reference

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A Highly Targeted Approach to Treating Atopic Dermatitis

A treatment that specifically targets IL-13 offers clinicians a way to help adult patients with moderate-to-severe disease

Atopic dermatitis (AD) arises from a complex pathophysiology, including environmental factors, genetic influences, acute and chronic inflammation, dysbiosis, and a perpetual itch-scratch cycle. Several Th2 cytokines, including interleukin IL-13 are drivers of inflammation in AD. IL-13 in particular, can offer a vital point of intervention for management of this chronic disease.1

As an integral part of the Th2 pathway that is central to the pathogenesis of AD, targeting IL-13 has been shown to help reduce clinical and molecular hallmarks of AD,” said Andrew F. Alexis, MD, MPH, Professor of Clinical Dermatology, Weill Cornell Medicine. “In my experience as a healthcare professional, I have seen patients who suffer from inadequate disease control experience meaningful improvements in their AD with the use of targeted treatments.”

Unmet Need in AD

More than half of AD patients worry over an impending flare, yet nonadherence to treatment plans is common, suggesting there is a need for improvement. There have been developments in the understanding of factors playing a role in the immune and inflammatory processes underlying AD signs and symptoms that will help improve the treatment landscape. 7-10

“AD is a persistent, unpredictable disease,” said Dr. Alexis. “Many adults with AD have difficulty maintaining adequate disease control, struggling with skin lesions and itching. There is a need for additional treatments when topical Rx therapies only go so far.”

INDEXATION AND IMPORTANT SAFETY INFORMATION

INDICATION

ADBRY™ (tralokinumab-ldrm) injection is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

• ADBRY is contraindicated in patients who have known hypersensitivity to tralokinumab-ldrm or any excipients in ADBRY.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.
With FDA approval of Adbry, clinicians and adult patients have a targeted biologic treatment option for the management of this chronic disease. It has demonstrated visible improvements in skin lesions and itch relief among patients in clinical trials at Week 16.5,11

Adbry was evaluated in three robust pivotal trials in nearly 2,000 adult patients with moderate-to-severe AD. Its approval was based on safety and efficacy results from the pivotal Phase 3 ECZTRA 1 and 2 monotherapy trials and ECZTRA 3 combination therapy with concomitant TCS as needed trial. In all three pivotal trials, Adbry 300 mg Q2W alone or with TCS as needed met the primary endpoints at Week 16, as measured by an Investigator Global Assessment score of clear or almost clear skin (IGA 0/1) or at least a 75% improvement in the Eczema Area and Severity Index score (EASI-75). Improvements in the secondary endpoint of itch reduction (4-point reduction in Worst Daily Pruritus NRS weekly average) also were observed at Week 16.11

- IGA 0/1: In ECZTRA 1 and 2, respectively, 16% and 21% of patients treated with Adbry 300 mg Q2W achieved IGA 0/1 at Week 16 vs 7% and 9% with placebo (P=0.002 and P=0.001, respectively). In ECZTRA 3, 31% of patients treated with Adbry 300 mg Q2W plus TCS achieved IGA 0/1 at Week 16 vs 27% with placebo plus TCS (P=0.033).11,10

- EASI-75: In ECZTRA 1 and 2, respectively, 25% and 35% of patients treated with Adbry 300 mg Q2W achieved EASI-75 at Week 16 compared with 15% and 10% (P=0.001 for both trials). In ECZTRA 3, 50% of patients treated with Adbry 300 mg Q2W plus TCS achieved EASI-75 at Week 16 vs 33% of patients with placebo plus TCS (P=0.002).11,10

- Worst Daily Pruritus NRS (weekly average): In ECZTRA 1 and 2, respectively, 20% and 24% of patients treated with Adbry 300 mg Q2W experienced itch reduction at Week 16 vs 10% and 9% with placebo (P=0.002 and P=0.001, respectively). In ECZTRA 3, 30% of patients treated with Adbry 300 mg Q2W plus TCS experienced itch reduction at Week 16 vs 31% with placebo plus TCS (P=0.399).11,10

**IMPORTANT SAFETY INFORMATION CONTINUED**

**WARNINGS AND PRECAUTIONS**

- **Hypersensitivity:** Hypersensitivity reactions, including anaphylaxis and angioedema have occurred after administration of ADBRY. If a serious hypersensitivity reaction occurs, discontinue ADBRY immediately and initiate appropriate therapy.

- **Conjunctivitis and Keratitis:** Conjunctivitis and keratitis occurred more frequently in atopically predisposed subjects who received ADBRY. Conjunctivitis was the most frequently reported eye disorder. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

- **Parasitic (Helminth) Infections:** Treat patients with pre-existing helminth infections before initiating treatment with ADBRY. If patients become infected while receiving ADBRY and do not respond to anthelmint treatment, discontinue treatment with ADBRY until the infection resolves.

- **Risk of Infection with Live Vaccines:** Avoid use of live vaccines during maintenance treatment with ADBRY. Complete all age appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines in patients treated with ADBRY. Limited data are available regarding coadministration of ADBRY with non-live vaccines.

**ADVERSE REACTIONS**

- **The most common adverse reactions (incidence ≥1%) are upper respiratory infections, conjunctivitis, injection site reactions, and eosinophilia.**

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** There are limited data from the use of ADBRY in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier, therefore, ADBRY may be transmitted from the mother to the developing fetus.

- **Lactation:** There are no data on the presence of tralokinumab-ldrm in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is present in breast milk. The effects of local gastrointestinal exposure and limited systemic exposure to ADBRY on the breastfed infant are unknown.

- **Pediatric Use:** The safety and effectiveness of ADBRY have not been established in pediatric patients.

Information for Colorado Prescribers: Pursuant to Colorado law, the wholesale acquisition cost information for Adbry is available at: https://www.leo-pharma.us/therapeutic-expertise/our-products.

**Long-Term Efficacy and Safety**

Clinical trials have also evaluated long-term efficacy and safety of Adbry to help patients and clinicians achieve lasting disease control. According to clinical trial results:

- Nearly 9 out of 10 responders at Week 16 treated with Adbry Q2W plus TCS as needed experienced lasting disease control at Week 32 as reported in ECZTRA 1.5,11

- More than half of responders at Week 16 treated with Adbry Q2W maintained IGA 0/1 and EASI-75 at Week 52, without any TCS use in a pooled analysis of ECZTRA 1 and a trial data.12

Adbry demonstrated long-term safety in five extensive clinical trials through 52 weeks. In ECZTRA 1, 2 and ECZTRA 3, the most common adverse events with Adbry (incidence ≥1% and greater than placebo) at Week 16 were upper respiratory tract infections (mainly reported as common cold), conjunctivitis, injection site reactions, and eosinophilia. In ECZTRA 1 and ECZTRA 2, the frequency of adverse reactions during maintenance treatment with Adbry 300 mg Q2W and Q4W, respectively, was 44% and 34%, in ECZTRA 3, it was 43% and 26%, respectively, with Adbry 300 mg Q2W and Q4W plus TCS as needed.13 In a pooled analysis of five trials, the incidence of conjunctivitis was 7.5% for Adbry (v1±1.582) vs 4.1% for placebo in the initial treatment period up to Week 16.12 Two cases of conjunctivitis led to discontinuation.12

Adbry is the only biologic for AD with a reduced maintenance dosing option, providing the flexibility to treat with Q2W or Q4W dosing after 16 weeks of treatment for patients achieving clear or almost clear skin, and who are less than 100 kg.13 To date, Adbry has been prescribed to more than 4,500 appropriate patients in the U.S.

Discover why Adbry can be your first-choice biologic for moderate-to-severe AD when topical Rx therapies only go so far. For additional information, visit https://www.adbryhcp.com/.

*Subjects who received rescue treatment or with missing data were considered non-responders.

§Responders were defined as subjects with an IGA 0 or 1 (“clear” or “almost clear”) or EASI-75 at Week 16. At Week 16, responders were re-randomized to Adbry 300 mg Q2W plus TCS or Adbry Q4W plus TCS for another 16 weeks.

*Responders were defined as subjects with an IGA 0 or 1 (“clear” or “almost clear”) or EASI-75 at Week 16. At Week 16, responders were re-randomized to Adbry 300 mg Q2W, Adbry Q4W, or placebo every other week for another 36 weeks.

**References:**


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MAT-59583 October 2022

For more information, visit https://www.adbryhcp.com.
INDICATION
ADBRY® (tralokinumab-ldrm) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATION
- ADBRY is contraindicated in patients who have known hypersensitivity to tralokinumab-ldrm or any excipients in ADBRY.

WARNINGS AND PRECAUTIONS
- **Hypersensitivity:** Hypersensitivity reactions, including anaphylaxis and angioedema have occurred after administration of ADBRY. If a serious hypersensitivity reaction occurs, discontinue ADBRY immediately and initiate appropriate therapy.
- **Conjunctivitis and Keratitis:** Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received ADBRY. Conjunctivitis was the most frequently reported eye disorder. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.
- **Parasitic (Helminth) Infections:** Treat patients with pre-existing helminth infections before initiating treatment with ADBRY. If patients become infected while receiving ADBRY and do not respond to antihelminth treatment, discontinue treatment with ADBRY until the infection resolves.
- **Risk of Infection with Live Vaccines:** ADBRY may alter a patient’s immunity and increase the risk of infection following administration of live vaccines. Prior to initiating therapy with ADBRY, complete all age appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines in patients treated with ADBRY. Limited data are available regarding coadministration of ADBRY with non-live vaccines.

ADVERSE REACTIONS
- The most common adverse reactions (incidence ≥1%) are upper respiratory infections, conjunctivitis, injection site reactions, and eosinophilia.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on following pages.
## Adbry—for lasting control and itch relief

**PATIENTS EXPERIENCED LASTING IMPROVEMENT FOR UP TO 52 WEEKS WITH ADBRY**

<table>
<thead>
<tr>
<th>Visible Skin Clearance and Itch Relief With Adbry at Week 16</th>
<th><strong>ADBRY MONOTHERAPY</strong></th>
<th><strong>COMBINATION THERAPY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECZTRA 1</strong></td>
<td><strong>ECZTRA 2</strong></td>
<td><strong>ECZTRA 3</strong></td>
</tr>
<tr>
<td>Adbry 300 mg Q2W</td>
<td>placebo</td>
<td>Adbry 300 mg Q2W</td>
</tr>
<tr>
<td>No. of patients randomized and dosed (FAS)*</td>
<td>601</td>
<td>197</td>
</tr>
<tr>
<td>IGA**</td>
<td>16% vs 7% (P=0.002)</td>
<td>21% vs 9% (P=0.001)</td>
</tr>
<tr>
<td>EASI-75**</td>
<td>25% vs 13% (P=0.001)</td>
<td>33% vs 10% (P=0.001)</td>
</tr>
<tr>
<td>No. of patients with baseline Worst Daily Pruritus NRS (weekly average) score ≥4</td>
<td>594</td>
<td>194</td>
</tr>
<tr>
<td>Worst Daily Pruritus NRS (24 point reduction)**</td>
<td>20% vs 10% (P=0.002)</td>
<td>25% vs 9% (P=0.001)</td>
</tr>
</tbody>
</table>

*Full Analysis Set (FAS) includes all subjects randomized and dosed.

**Responders were defined as subjects with an IGA 0 or 1 ("clear" or "almost clear").

EASI=Eczema Area and Severity Index; IGA=Investigator’s Global Assessment; NRS=Numeric Rating Scale; TCS=topical corticosteroids.

**NEARLY 9 OUT OF 10 RESPONDERS AT WEEK 16 EXPERIENCED LASTING DISEASE CONTROL AT WEEK 32 WITH ADBRY 300 MG Q2W+TCS AS NEEDED**

<table>
<thead>
<tr>
<th>ECZTRA 3</th>
<th>Adbry Q2W+TCS as needed</th>
<th>Percentage of patients who maintained response at Week 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16</td>
<td>Week 32</td>
<td></td>
</tr>
<tr>
<td>92%</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>EASI-75 (60/65)</td>
<td>IGA 0/1 (40/45)</td>
<td></td>
</tr>
</tbody>
</table>

More than half of responders at Week 16 maintained response at Week 52 with Adbry Q2W monotherapy, without any TCS use:**

- **ECZTRA 1**: IGA 0/1 and EASI-75 response was maintained by 51% (20/39) and 60% (28/47) of patients on Adbry Q2W, respectively; 47% (9/19) and 33% (10/30) of patients on placebo maintained response.

- **ECZTRA 2**: IGA 0/1 and EASI-75 response was maintained by 60% (32/53) and 57% (43/76) of patients on Adbry Q2W, respectively; 23% (6/26) and 20% (8/40) of patients on placebo maintained response.

**Responders were defined as subjects with an IGA 0 or 1 ("clear" or "almost clear") or EASI-75 at Week 16. At Week 16, responders (defined as subjects with an IGA 0 or 1 or EASI-75 at Week 16) were rerandomized to Adbry 300 mg Q2W with TCS or Adbry Q4W with TCS for another 16 weeks.

**Subjects who received rescue treatment or with missing data at 16 weeks were considered as nonresponders.

**Study designs**

The efficacy and safety of Adbry were assessed in 3 randomized, double-blind, placebo-controlled trials with a total of 1934 patients 18 years of age and older, with moderate-to-severe atopic dermatitis not adequately controlled by topical medications. In ECZTRA 1, 2, and 3, subjects received subcutaneous injections of Adbry 600 mg or placebo on Day 0, followed by Adbry 300 mg or placebo Q2W for 16 weeks. In ECZTRA 3, patients received concomitant TCS as needed (mometasone furoate 0.1% cream was dispensed at each dosing visit). ECZTRA 1, 2, and 3 assessed the primary endpoints of the proportion of subjects with an IGA 0 or 1 at Week 16 and the proportion of subjects with EASI-75 at Week 16. Secondary endpoints included the reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 points on the 11-point itch NRS from baseline to Week 16.

**At Week 16, patients with an IGA 0/1 or EASI-75 response were re-randomized to Adbry Q2W, Q4W, or placebo for another 36 weeks (ECZTRA 1, 2) and Q2W or Q4W for another 16 weeks (ECZTRA 3).**

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

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy**: There are limited data from the use of ADBRY in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, ADBRY may be transmitted from the mother to the developing fetus.

- **Lactation**: There are no data on the presence of tralokinumab-ldrm in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is present in breast milk. The effects of local gastrointestinal exposure and limited systemic exposure to ADBRY on the breastfed infant are unknown.

- **Pediatric Use**: The safety and effectiveness of ADBRY have not been established in pediatric patients.
When topical Rx therapies only go so far

Start with Adbry and see progress continue

Adbry is the first and only biologic to specifically target and neutralize IL-13

Adbry demonstrated significant skin clearance, improvements in lesion extent and severity, and itch relief at Week 16, and was studied for long-term control at Weeks 32 and 52

Demonstrated long-term safety through 52 weeks

- Most common adverse reactions (AR) (incidence ≥1%) for Adbry vs placebo (ECZTRA 1 and ECZTRA 2 pooled) and Adbry + TCS vs placebo + TCS (ECZTRA 3), respectively, at Week 16 are upper respiratory tract infections (23.8% vs 20.4%, 30% vs 15.4%), conjunctivitis (7.5% vs 3.1%, 13.6% vs 4.9%), injection site reactions (7.4% vs 4.1%, 11.1% vs 0.8%), and eosinophilia (1.4% vs 0.5%, 1.2% vs 0%)
- The safety profile of Adbry during maintenance treatment was consistent with that in the initial 16-week treatment period. In addition, the frequency of adverse reactions with Adbry Q2W and Q4W in ECZTRA 1 and ECZTRA 2 was 44% and 34%, respectively, and 43% and 26% with Adbry + TCS Q2W and Q4W in ECZTRA 3, respectively

The flexibility to treat with Q2W or Q4W dosing

- An initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections)
- Maintenance dose of 300 mg (2 prefilled syringes) Q2W
- Q2W or Q4W dosing may be considered in patients <100 kg (220 lb) who achieve “clear” or “almost clear” skin after 16 weeks of treatment

Adbry has no boxed warning, and no requirement for initial lab testing or ongoing lab monitoring in the Prescribing Information. Adbry is a targeted biologic therapy and is not an immunosuppressant or a steroid

IMPORTANT SAFETY INFORMATION (cont’d)

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

You may also report side effects to LEO Pharma Inc. at 1-877-494-4536, option 1, or email to usdrugsafety@leo-pharma.com

Please see Brief Summary of Prescribing Information on next page.

FIND OUT MORE ABOUT ADBRY: Visit AdbryHCP.com

ADBR™ (tralokinumab-ldrm) injection, for subcutaneous use

**INDICATIONS**

In the monotherapy trials (ECTRA 1 and ECTRA 2) through Week 16, the proportion of subjects with at least a 75% improvement in EASI due to adverse reactions was 0.7% in the ADBRY 300 mg every other week group and 0% in the placebo group. In the combination trials (ECTRA 1 and ECTRA 2) through Week 16, the proportion of subjects with adverse reaction due to adverse reactions was 0.8% in the ADBRY 300 mg every other week + TCS group and 0% of the placebo + TCS group. The most common adverse reactions leading to discontinuation in the ADBRY group compared to the placebo group were injection-site reaction (2.8% vs 0.3%) and eosinophilia (0.3% vs 0%) in ECTRA 1 and ECTRA 2, and injection-site reaction (4.5% vs 0%) and conjunctivitis (0.4% vs 0%) in ECTRA 3.

**SAFETY:**

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

• An initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) per 2 weeks (Q2W) or per 4 weeks (Q4W). The flexibility to treat with Q2W or Q4W dosing.

Adbry demonstrated significant skin clearance, improvements in lesion extent and severity, and reductions in Itch Numeric Rating Scale and Sleep Interference Score compared to placebo. In ECZTRA 3, 65% of subjects treated with ADBRY 300 mg every 4 weeks had complete clearance of lesions, compared to 39% of subjects treated with placebo. ADBRY 300 mg every 4 weeks achieved a greater proportion of subjects with at least 75% improvement in EASI and IGA compared to placebo, with a numerical advantage of approximately 15%.

**FIND OUT MORE ABOUT ADBRY:** Visit AdbryHCP.com

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**When topical Rx therapies only go so far**

**INDICATIONS AND USAGE**

ADBRY was administered as 300 mg every other week (Q2Wc) or monthly (Q4W) subcutaneous injections of ADBRY, with or without concurrent topical corticosteroids (TCS). A total of 180 subjects were treated with ADBRY for at least 1 year.

In these 3 atopic dermatitis trials, 1064 subjects were treated with subcutaneous injections of ADBRY with or without concurrent topical corticosteroids (TCS). A total of 817 subjects were treated with ADBRY for at least 1 year.

In ECTRA 1 and ECTRA 2, Adbry was compared to the safety of the ADBRY monotherapy treatment to placebo through Week 52. ECTRA 3 compared the safety of ADBRY + TCS to placebo + TCS through Week 32.

**CONTRAINDICATIONS**

Adverse reactions are discussed in greater detail elsewhere in this Brief Summary. ADBRY must not be administered to:

- Hypersensitivity or a previous adverse reaction to ADBRY, or to any of the components of ADBRY.
- Patients known to be pregnant or who are breastfeeding.

**ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail elsewhere in this Brief Summary.

- Hypersensitivity
- Conjunctivitis and Keratitis

**Clinical Trial 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.

The safety of ADBRY was evaluated in a pool of 5 randomized, double-blind, placebo-controlled trials in adult subjects with moderate-to-severe atopic dermatitis including three phase 3 Eczema Trakline trials (ECTRA 1, ECTRA 2, and ECTRA 3), a dose-finding trial, and a vaccine response trial.

The safety of ADBRY has been established in pediatric patients.

The safety and effectiveness of ADBRY have not been established in pediatric patients.

**Pediatric Use**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

There are no data on the safety of tralokinumab-ldrm in human milk, although similar products have been reported. It is not known whether breastfeeding would be considered through the mother’s clinical need for ADBRY and any potential adverse effects on the breast milk from ADBRY or from the underlying maternal condition.

**Lactation**

Advise patients that ADBRY may increase the risk of infection following vaccines. In clinical trials, ADBRY was well tolerated when given concurrently with live vaccines.

The safety of ADBRY has been established in pediatric patients.

**GERIATRIC USE**

**OVERDOSAGE**

There is no appropriate treatment for ADBRY overdose. In the event of overdose, contact Poison Control (1-800-222-1222) for latest recommendations and monitor the patient for any signs or symptoms of adverse reactions and institutes appropriate symptomatic treatment immediately.

**PATIENT COUNSELING INFORMATION**

Advising patients to report any adverse events on the breastfed child from ADBRY or from the underlying maternal condition.

**Advising patients to consider discontinuing ADBRY and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions.**

**CONTRAINDICATIONS**

Advising patients to consider discontinuing ADBRY and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions.

**ALLERGIC REACTIONS**

**Manufactured by:** LEO Pharma A/S, Industriparken 55, Ballerup, Denmark DK-2750

**Distributed by:** LEO Pharma Inc. Madison, NJ 07940, USA

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New Directions in the Treatment of Basal Cell Carcinoma

Two dermatologists discuss how immune checkpoint inhibitors will change the way dermatologists manage skin cancer.

Kaitlyn Bader, Associate Editor

In the treatment of basal cell carcinoma (BCC), “The name of the game is identifying the lesions early on and then treating them accordingly, right? A lot of what I hear is, ‘Hey, doc, if it’s not going to kill me, it’s slow growing, why should I take care of it? Why should I bother doing anything?’ Then usually I show them one picture of what an advanced basal cell cancer can look like, and they’re ready to begin treatment,” said Sherrif F. Ibrahim, MD, PhD, an associate professor in the Department of Dermatology at the University of Rochester Medical Center in New York.

“Ibrahim and Patel both noted that they’re seeing an increasing incidence of BCC, especially in younger patients. Patel explained that BCC is the most common type of skin cancer worldwide, and that BCC is a unique type of cancer. Despite the variety of BCC presentations, the majority of them are managed with early intervention. Globally, practice variations may be changing, but the commonality of the disease makes it easier to recognize and treat.

In most cases, surgery is the gold-standard treatment for BCC, but factors such as the size and location of the cancer influence a patient’s treatment path. Age is another consideration because younger patients may not be inclined to choose surgery that can result in scars. No matter the case, early identification is key.

Both dermatologists agreed on the importance of the multidisciplinary tumor boards at their respective institutions. They explained that these boards bring together dermatologists, oncologists, and other surgeons to discuss the best course of action for BCC treatment and that these discussions are particularly helpful considering the increase in advanced BCC cases.

They noted that if surgery is not the immediate choice, Hedgehog inhibitors are effective but come with unwanted adverse effects (AEs), such as hair loss, muscle pains, and loss of taste.

Ibrahim then mentions an alternative BCC treatment—one that’s seen an increased use in dermatology—immune checkpoint inhibitors. Immune checkpoint inhibitors block checkpoint proteins from binding with their partner proteins. This prevents the “off” signal from being communicated so that the body’s T cells can kill cancer cells. For patients who are unable to tolerate the AEs of Hedgehog inhibitors, cemiplimab-rvcl (Libtayo), a PD-1 immune checkpoint inhibitor, offers hope for an alternative and more tolerable treatment.

“We’re really excited, here, in the field of dermatology, about immune checkpoint therapy, specifically the PD-1 inhibitor pathway, and it’s been exciting to see that for melanoma initially and then [for] Merkel cell carcinoma, squamous cell carcinoma, [and] now basal cell carcinoma,” Patel said.

Cemiplimab has prompted dermatologists and oncologists to rethink their approach to locally advanced BCC in patients who have either failed Hedgehog therapy or for whom it is not ideal. Patel noted that the response rate for immune checkpoint inhibitors is in the 20% to 30% range for locally advanced or metastatic BCC.

Ibrahim agreed that the response rates for immune checkpoint inhibitors are encouraging because they are reasonably high from an oncology perspective. Because excision and Hedgehog inhibitors were previously the only viable treatment options for BCC, and they are not always successful, immune checkpoint inhibitors address the current gap in care for BCC.

“Of course, there are safety considerations when we’re using any kind of immunotherapy and immune checkpoint inhibitors. That’s a whole other conversation that we have to have with our patients,” Ibrahim said. “But for the most part, we know that these medications are very well tolerated. At that point, when the patient has or we as practitioners have felt that the Hedgehog inhibitor’s no longer an ideal treatment for that patient, it’s really nice to have an additional, completely different category of medications and class of agents that we can use.”

Regarding safety considerations for cemiplimab, Patel noted that 90% of patients tolerate the drug well. For the 10% of patients who experience AEs, other medications can be added or the cemiplimab dosing can be adjusted to help reduce AEs.

“Immune checkpoint inhibitors are game changers. They really are the holy grail to oncology,” Patel said. “We’re seeing that across cancer types. We saw that in squamous cell carcinoma in a much higher rate than in basal cell carcinoma. But now we have an option for patients that really had nothing—[just] chemotherapy and radiation, that are really not great for this nonresponsive tumor type. And we’re excited to see what will come down the pipeline with dual combination.”

Patel and Ibrahim agreed that immune checkpoint inhibitors will change the way dermatologists treat BCC. For example, in patients who have a suppressed immune system or have received organ transplants, cancer can wreak havoc on their bodies. Now with immune checkpoint inhibitors like cemiplimab, more options are available for these patients who would, oftentimes, be debilitated by cancer. Immune checkpoint inhibitors will put control back in the hands of dermatologists to effectively and safely treat BCC.

Reference
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Preventing Misdiagnosis of Rare Skin Diseases

Thorough history taking is essential during the consultation and can help clinicians rule out other potential differential diagnoses.

Ilya Petrou, MD, Staff Correspondent

When it comes to diagnosing unusual dermatologic diseases, a careful history from the patient and a close eye for diagnostic work-up detail can help shorten the road from A to B for diagnostic treatment and management path.

This article offers strategies to help prevent misdiagnosis of 2 rare skin diseases: Merkel cell carcinoma and actinic prurigo.

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare, aggressive form of skin cancer. Approximately 3000 new cases of MCC are diagnosed annually in the United States. Tumors from MCC usually occur in sun-exposed areas, are common on the head and neck of older White men, and carry a high risk of recurrence and metastasis. The main risk factors for MCC include UV exposure, advanced age, and immunosuppression, and the development of MCC is associated with the Merkel cell polyomavirus.

Although the lesion itself can appear suspicious to the astute clinician, many dermatologists may miss the diagnosis upon first examination, according to Paul Nghiem, MD, PhD, professor and head of the Division of Dermatology and the George F. Odland Endowed Chair in Dermatology at the University of Washington in Seattle.

“Statistics show that even dermatologists get the clinical diagnosis of MCC wrong the majority of the time,” Nghiem said. “The main challenge is to decide that a biopsy needs to happen. Most dermatologists who biopsy an MCC will be surprised by the pathology report because MCC does not have a specific appearance and it is uncommon.”

In a systematic cohort study of 195 patients diagnosed with MCC between 1980 and 2007, Nghiem and colleagues aimed to define the clinical characteristics of MCC to identify features that may help clinicians better recognize the aggressive skin cancer. Their findings showed that 88% of MCCs were asymptomatic (nontender)—despite rapid growth in the prior 3 months (63% of lesions) and being red or pink (56%). In addition, 56% of lesions were presumed to be benign, with a cyst or acneiform lesion being the most common diagnosis given (32%), followed by lipoma (6%) and dermatofibroma (5%). According to Nghiem, almost all patients with MCCs will have 3 or 4 clinical features in AEOU. He noted, however, to be cautious because these characteristics are not MCC specific and may apply to other lesions. A biopsy will be telling.

“If you’ve got an older patient who is immunosuppressed and has a history of non-melanoma skin cancer...and sun-damaged skin and presents with a suspicious quickly growing nodule on the skin, a biopsy should be performed and will likely be definitive,” Nghiem said.

Performing a biopsy early on is advantageous because, according to Nghiem, the cancer will have already spread beyond the primary site in more than one-third of cases. Therefore, it is paramount to treat MCC appropriately soon after the diagnosis is made.

The management of MCC is more complicated than any other skin cancer, but fortunately, there is increasing agreement in many aspects of how MCC should be managed. Nghiem noted that MCC management should follow a multidisciplinary approach. Surgery is often, but not always, the first step in treatment. Unlike melanoma, a full work-up for staging (full body scan and usually a sentinel lymph node biopsy) is indicated in almost all cases before deciding on therapy because the tumor will have spread beyond the primary site in almost half of cases.

“Clinicians should be wary and have a lower threshold to perform a biopsy in patients with prior skin cancers and a nontender lesion arising on sun-exposed skin, especially if the immune system is compromised,” Nghiem said. “Even if you’re not thinking about MCC upon first examination, such features should be of concern and make the clinician lean toward biopsy.”

Actinic Prurigo

Also having UV exposure in its pathogenesis, actinic prurigo is another rare dermatologic disease that is challenging to treat and manage. A rare form of idiopathic photodermatosis, actinic prurigo primarily affects sun-exposed areas, including the face, neck, dorsal surface of the upper extremities, lips, and conjunctival mucosa. The disease follows a chronic course, with patients typically presenting with indurated, intensely pruritic erythematous papules, nodules, and excoriated plaques on sun-exposed areas of the skin.

“When a patient presents with an intensely pruritic skin eruption that’s restricted to sun-exposed areas, derma-
tologists need to think of all the differential diagnoses related to photosensitive sun-induced reactions,” said Bernard A. Cohen, MD, a professor of dermatology and pediatrics at Johns Hopkins University School of Medicine in Baltimore, Maryland. “Given the fact that actinic prurigo is persistent, sometimes lasting for months, can recur, or [that] the patient [may continue] to get sun exposure, it can be a horribly itchy, life-compromising reaction.”

Current histological and research findings suggest that actinic prurigo is an ongoing type 4 hypersensitivity reaction with still unknown other immunopathogenic processes, including the involvement of the HLA-DR4 gene; the infiltration of CD4 lymphocytes, eosinophils, and mast cells; and a serum increase in IgE. Lesions appear hours or days after sun exposure (long- and short-wave UV-A and UV-B), which is contrary to the course of solar urticaria, in which skin lesions appear only minutes after UV exposure.

“Actinic prurigo may look a little urticarial at first, but it is persistent and will not disappear easily within 24 hours like urticaria would,” Cohen said. “Solar urticaria is something that lasts just minutes to hours, certainly less than 24 hours by definition, whereas actinic prurigo will be persistent and continue to spread and may eventually even involve areas that are not sun-exposed, such as the buttocks.”

The main differential diagnosis of actinic prurigo is polymorphous light eruption, followed by atopic dermatitis with photosensitivity and solar urticaria. Although actinic prurigo can affect people of all ages, approximately one-third of patients are children, with boys and girls being equally affected. In adult-onset actinic prurigo, however, women are affected 2 times more often than men.

Because many patients first develop symptoms during childhood, Cohen said the main clinical consideration to rule out in this younger population is atopic dermatitis with photosensitivity. In adults, photoallergic contact dermatitis and chronic actinic dermatitis are other dermatologic conditions that need ruled out in patients presenting with photosensitivity of a chronic nature.

Meticulous history taking is requisite during the consultation and can help clinicians rule out other potential differential diagnoses. Contrary to polymorphous light eruption and other dermatoses in which UV and photosensitivity play a central role in disease pathogenesis, actinic prurigo will be different particularly in its long-term persistence and can progress even though patients protect themselves from sunlight. Nevertheless, disease management for actinic prurigo begins with sun protection and sunlight avoidance.

Early diagnosis and proper management are key to help limit patient morbidity. Current treatments include topical antihistamines, corticosteroids, emollients, and photochemotherapy, as well as systemic therapies for severe cases.

“Topical corticosteroids are the first-line therapy, and to optimize treatment outcomes, it is crucial to apply them in the beginning when lesions first appear,” Cohen said. “The earlier you recognize the symptoms, the earlier you can start an aggressive topical therapy, [and] the better the chances of effectively treating actinic prurigo.”

Reference
INDICATION

OPZELURA is indicated for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

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

OPZELURA was studied in 2 double-blind, randomized, vehicle-controlled trials of identical design that enrolled 674 adult and adolescent patients with nonsegmental vitiligo ≥12 years of age. Patients had depigmented areas affecting ≥0.5% facial body surface area (F-BSA), ≥3% nonfacial BSA, and total body vitiligo area (facial and nonfacial) of up to 10% BSA. Patients with complete leukotrichia within any facial lesion were excluded. Phototherapy was not permitted during the trials. In both trials, patients were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily (BID) for 24 weeks followed by a 28-week open-label extension, wherein patients originally assigned to vehicle could switch to OPZELURA.1,4

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

Nearly 1 in 3 patients achieved at least 75% improvement in the facial vitiligo area scoring index* (F-VASI75) at 24 weeks (primary endpoint; 29.9% vs. 7.5% (P < 0.0001) and 29.9% vs. 12.9% (P < 0.01)).

Data from an open-label extension at Week 52 showed that approximately half of the patients remaining in the study who applied OPZELURA from Day 1 achieved F-VASI75 at 52 weeks: ≈51% for OPZELURA and ≈28% for vehicle-to-OPZELURA (Week 24 to Week 52). Data were reported as observed.

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 cryptococcosis and pneumocystosis.
• Bacterial, viral, including herpes zoster, 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.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. 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.

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. (cont. on next page)
OPZELURA was studied in 2 double-blind, randomized, vehicle-controlled trials of identical design that enrolled 674 adult and adolescent patients with nonsegmental vitiligo ≥12 years of age. Patients had depigmented areas affecting ≥0.5% facial body surface area (F-BSA), ≥5% nonfacial BSA, and total body vitiligo area (facial and nonfacial) of up to 10% BSA. Patients with complete leukotrichia within any facial lesion were excluded. Phototherapy was not permitted during the trials. In both trials, patients were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily (BID) for 24 weeks followed by a 28-week open-label extension, wherein patients originally assigned to vehicle could switch to OPZELURA.1,4

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

*The facial vitiligo area scoring index (F-VASI) is a composite measurement of the overall area of facial vitiligo patches and degree of depigmentation within patches. As assessed, the face did not include surface area of the lips, scalp, or ears.5

†P-values from exact logistic regression: [response at Week 24 = treatment + stratification factors (Fitzpatrick skin type I and II vs. Fitzpatrick skin type III, IV, V, and VI, Region North America/Europe)].3

‡52-week data were reported as observed. Therefore, no conclusions of safety or efficacy should be made based on these results.

Now you can prescribe OPZELURA, the **FIRST + ONLY FDA-APPROVED** treatment for nonsegmental vitiligo repigmentation. Proven results with a topical.1

**F-VASI 75 AT 24 WEEKS**

Nearly 1 in 3 patients achieved at least 75% improvement in the facial vitiligo area scoring index* (F-VASI75) at 24 weeks (primary endpoint; 29.9% vs. 7.5% (P < 0.0001) and 29.9% vs. 12.9% (P < 0.01))5†

Data from an open-label extension at Week 52

**F-VASI 75 AT 52 WEEKS**

About half the patients remaining in the study who applied OPZELURA from Day 1 achieved F-VASI75 at 52 weeks: ≈51% for OPZELURA and ≈28% for vehicle-to-OPZELURA (Week 24 to Week 52). Data were reported as observed.5‡

OPZELURA was studied in 2 double-blind, randomized, vehicle-controlled trials of identical design that enrolled 674 adult and adolescent patients with nonsegmental vitiligo ≥12 years of age. Patients had depigmented areas affecting ≥0.5% facial body surface area (F-BSA), ≥5% nonfacial BSA, and total body vitiligo area (facial and nonfacial) of up to 10% BSA. Patients with complete leukotrichia within any facial lesion were excluded. Phototherapy was not permitted during the trials. In both trials, patients were randomized 2:1 to treatment with OPZELURA or vehicle cream twice daily (BID) for 24 weeks followed by a 28-week open-label extension, wherein patients originally assigned to vehicle could switch to OPZELURA.1,4

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

*The facial vitiligo area scoring index (F-VASI) is a composite measurement of the overall area of facial vitiligo patches and degree of depigmentation within patches. As assessed, the face did not include surface area of the lips, scalp, or ears.5

†P-values from exact logistic regression: [response at Week 24 = treatment + stratification factors (Fitzpatrick skin type I and II vs. Fitzpatrick skin type III, IV, V, and VI, Region North America/Europe)].3

‡52-week data were reported as observed. Therefore, no conclusions of safety or efficacy should be made based on these results.

**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 cryptococcosis and pneumocystosis.
- Bacterial, viral, including herpes zoster, 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.

Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib.

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.

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. (cont. on next page)

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, on following pages.
THROMBOSIS
Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately.

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
In nonsegmental vitiligo, the most common adverse reactions (incidence ≥ 1%) are application site acne (6%), application site pruritus (5%), nasopharyngitis (4%), headache (4%), urinary tract infection (2%), application site erythema (2%), and pyrexia (1%).

Pregnancy
There is 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.

Lactation
Advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5–6 elimination half-lives).

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, on following pages.
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 treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older.

Limitations 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 extra pulmonary disease.
- **Invasive fungal infections**, including cryptococcosis, and pneumocystosis.
- **Bacterial, viral, including herpes zoster**, and other infections due to opportunistic pathogens.

Avoid use of OPZELURA in patients with a known history of these events prior to initiating or continuing therapy with OPZELURA.

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

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiac death, was observed in patients treated with the JAK inhibitor compared to TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

**MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)**

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers.

Discontinue OPZELURA in patients who are current or past smokers who are at increased risk [see Warnings and Precautions].

**THROMBOSIS**

Thromboembolic events were observed in trials with OPZELURA. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor, a higher rate of thrombosis was observed compared to TNF blockers. Avoid OPZELURA in patients at risk. If symptoms of thrombosis occur, discontinue OPZELURA and treat appropriately [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.

**Mortality:** In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiac death, was observed in patients treated with the JAK inhibitor compared to TNF blockers. 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 JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies. 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 when on treatment, 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. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

**Major Adverse Cardiovascular Events (MACE):** In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. 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 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 they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

**Thrombosis:** Thromboembolic events were observed in clinical trials with OPZELURA. Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been reported in patients receiving JAK inhibitors used to treat inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers. Avoid OPZELURA in patients who may be at an increased risk of thrombosis. If symptoms of thrombosis occur, discontinue OPZELURA and evaluate and treat patients appropriately.

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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 (TRuE-V1 and TRuE-V2), 449 adult and pediatric subjects 12 years of age and older with nonsegmental vitiligo were treated with OPZELURA twice daily for 24 weeks. In the OPZELURA group, 55% of subjects were females, and 81% of subjects were White, 5% were Black, and 4% were Asian. The adverse reactions reported by OPZELURA treated subjects with an incidence of ≥ 1% and at least 1% greater incidence than in the vehicle arm in the 24-week double-blind period are as follows (OPZELURA [N-449] vs Vehicle [N=224], respectively): Subjects with any treatment emergent adverse event (TEAE) 214 (48%) vs 79 (35%), Application site acne 26 (6%) vs 2 (1%), Application site pruritus 23 (5%) vs 6 (3%), Nasopharyngitis 19 (4%) vs 5 (2%), Headache 17 (4%) vs 6 (3%), Urinary tract infection 7 (2%) vs 1 (<1%), Application site erythema 7 (2%) vs 1 (<1%), and Pyrexia 6 (1%) vs 0 (0%).

Adverse reactions that occurred in TRuE-V1 and TRuE-V2 ≥ 0.5% to < 1% of subjects in the OPZELURA group and none in the vehicle group were: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, dermatitis, edema, ear infection, gastritis, gastrinomas, gastritis, gastroenteritis, headache, influenza-like illness, insomnia, nasopharyngitis, and vomiting.

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.

Clinical Trials: 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 is 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: 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% atopic dermatitis-affected 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 is 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 5-6 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 radioactive milk in was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and stable metabolites in milk, and the ratio of drug to parent compound was not significantly different than in maternal plasma.

Pediatric Use: Nonsegmental Vitiligo: The safety and effectiveness of OPZELURA for the topical treatment of nonsegmental vitiligo have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-V1 and TRuE-V2, which included 55 pediatric subjects aged 12 to 17 years with nonsegmental vitiligo. 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 with nonsegmental vitiligo have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measurements. 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 831 total subjects enrolled with nonsegmental vitiligo in clinical trials with OPZELURA, 65 (8%) were 65 years of age and older. Clinical trials of OPZELURA in subjects with nonsegmental vitiligo did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

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 [see Warnings and Precautions].

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. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen [see Warnings and Precautions].

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 [see Warnings and Precautions].

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 [see Warnings and Precautions].

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].

Advises patients to limit treatment to one 60 gram tube per week or one 100 gram tube per 2 weeks [see Dosage and Administration].

Inform patients to promptly 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 about four weeks after the last dose [see Use in Specific Populations].

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

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The Role of Non-prescription Products in the Management of Acne

Help educate your patients by watching the latest acne series, Between the Lines: The Role of Non-Prescription Products in the Management of Acne!

In this 8-part series, industry experts Joshua Zeichner, MD, and Mona Gohara, MD, dive deep into issues that your patients may face and provide valuable insight on OTC treatments that will improve the management of their conditions.

Expand your knowledge of different OTC cleansers and moisturizers, including their role in skin barrier destruction and how to offset it.
Innovation Leads to Dermatology Trailblazers

Research and development are resulting in new treatment options for major conditions

Iya Petrou MD, Staff Correspondent

Exciting developments in the treatment and management of numerous dermatologic diseases are providing much-needed options to adult and pediatric patients with these conditions. New biologics and Janus kinase (JAK) inhibitors offer viable therapeutic choices for an increasing list of dermatologic diseases and conditions, including atopic dermatitis, alopecia areata, psoriasis, vitiligo, and other common dermatoses.

Although the scope of cutaneous conditions and diseases in dermatology is extensive, continued research and development have led to several breakthrough medications to address many common dermatologic diseases.

“In the past 20 years of being involved in dermatology, I have never seen so much innovation and so much of a deep understanding of diseases. I think we have entered the ‘virtuous cycle of drug development,’ where we innovate and make new medicines, learn more about the disease, and then make even better medicines with more targeted actions,” said Peter A. Lio, MD, FAAD, clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine, founding director of Chicago Integrative Eczema Center, and founding partner of Medical Dermatology Associates of Chicago in Illinois.

“The addition of these excellent therapeutic choices for the entire spectrum of atopic dermatitis has complicated—in a good way—the...
treatment and management of the disease," Lio said. "Along with the windfall from all of these new topical and oral medications comes a world of questions in terms of what agent to use and in which scenario. Going forward, we need to discuss the safety of the medications with our patients and carefully determine their optimal treatment plan while understanding the risk factors for each individual patient."

In dermatology and, in particular, pediatric dermatology, very few treatments are approved for the tremendous range of diseases. As such, many dermatologists have been relegated to live in an off-label world because they know certain medications that lack of FDA approval for an indication or age group could help their patients. According to Lio, the FDA seems to have turned its focus more on children, so pediatric dermatology has benefited recently with the approval of novel medications for younger age groups.

"I am very excited that dupilumab [Dupixent] is now approved down to 6 months of age," Lio said. "The hope is that we are going to see a number of safe and effective medications that will be made available for a very young pediatric age group, which is hugely important for those physicians who regularly see in the pediatric population."

**Coverage Concerns**

Although novel therapeutic agents and drug vehicles for dermatologic diseases have become available on a global scale, insurance providers and health care coverage remain a major obstacle.

"In the last couple of years, we have seen an explosion of new targeted drugs such as dupilumab, which is now the standard of care in most parts of the world," said Maria Teresa Garcia-Romero, MD, MPH, chair of the International Outreach and Global Alliances Committee for the Society for Pediatric Dermatology and an attending physician and assistant professor at the National Institute of Pediatrics in Mexico City, Mexico. "However, in my region in Latin America, the introduction and approval of this agent as well as other breakthrough medications are still in their beginning stages, and it can be very challenging for patients to receive insurance coverage for these very effective therapies."

Garcia-Romero said it usually takes 3 to 5 years for these medications, including the IL-17 blocker ixekizumab (Taltz) and IL-12/23 blocker ustekinumab (Stelara) used for psoriasis, to become available in Mexico and other Latin American countries, significantly lagging behind the relatively quicker FDA approval for these medications in the United States. Once approved however, pediatric patients will still have difficulty attaining these agents due to lack of appropriate insurance coverage.

"The accessibility of these drugs is still very difficult, and most patients cannot pay for these medications themselves," Garcia-Romero said. "Only those patients who have medical insurance or visit hospitals where government-subsidized plans cover the costs of therapy have access to these drugs. As with other countries, in Latin America, unfortunately it is the regulatory environment that hinders patients from [receiving these drugs in a timely manner]."

In addition, many dermatologic diseases and conditions still need to be more urgently addressed, such as alopecia areata, vitiligo, and acne, as well as genodermatoses including congenital ichthyosis and epidermolysis bullosa, the latter of which has almost fully unmet needs. According to Garcia-Romero, some of these diseases for which there isn’t any FDA-approved medication have been experimentally and successfully treated in the past few years with biologics and other targeted therapies. However, repeated attempts to have insurance companies cover the medications for these conditions and diseases have failed. Lio noted, oftentimes leaving patients with the bill or with less optimal treatment options to choose from.

Lio added that this can contribute to burnout and exhaustion of clinicians and their patients when seeking optimal therapies.

**What’s Next?**

"I think some of the next frontiers for novel therapeutic approaches in dermatology are alopecia areata and vitiligo," Lio said. "Although neither of these diseases have a single FDA-approved treatment to date, I am optimistic that by the end of this year, we will have a working viable treatment for these common dermatologic conditions, likely with the JAK inhibitors leading the way."

Lio added that as more treatment options become available, it is of paramount importance that the decision-making process regarding treatment and management be shared with the patient. Lio explained that, ideally, clinicians should lay out the potential therapeutic options and carefully review them with the patient when deciding on a treatment plan. Lio said this becomes even more important when dealing with more serious medications because patients must be ready and willing to address any adverse effects that may occur during the treatment period.

"This is a very exciting time in pediatric dermatology and adult dermatology," Garcia-Romero said. "There are many areas of research in inflammatory disorders and genetic disorders where in the past 10 years, we have seen more advances than in the previous decades. We are getting closer to being able to treat many of the conditions that we see on a daily basis, and we can provide a lasting improvement for patients."

Lio agreed. "We are currently in an innovation phase of development, and it has been such an exciting bonanza of new ideas and therapies that have recently come forth," he said. "The next 10 years should be very interesting, and surely our patients will benefit from continuing research in dermatology."

"In the past couple of years, we have seen an explosion of new targeted drugs."

Maria Teresa Garcia-Romero, MD, MPH
Pediatric Nail Disorders

Management differs from adults and requires a meticulous examination to rule out underlying diseases.

Fazila Rajab, Staff Correspondent

Nail disorders among infants and children are a relatively uncommon observance in pediatric dermatology, but when they do appear, they can be associated with a systemic condition or a cosmetic or psychological problem. Their prevalence varies among different populations. A study published in Turkey has found the incidence rate of nail disorders to be 4.4% in pediatric patients. Their management strategy differs from the strategy for adults and requires a thorough examination to rule out any underlying diseases.

Understanding the normal nail anatomy is vital for understanding nail disease. The nail plate, a keratinized structure, is attached to the vascularized nail bed at the hyponychium, paronychium, eponychium, and cuticle. The cuticle prevents foreign objects from entering the nail matrix, an epithelial structure beneath the nail. The lunula is the visible distal part of the nail matrix.

What follows are several nail conditions that may be seen in a pediatric dermatology practice.

Koilonychia

Koilonychia, commonly known as spoon nails, causes the nails to become abnormally concave. When a nail is in this state, it might look like it has been scooped out because of its pliable nature. The condition is prevalent among 33% of neonates and usually goes away on its own within the first decade of life when the nail plate strengthens.

If it does not go away, the culprits of koilonychia are usually injury, inflammatory dermatosis, or iron deficiency anemia. Most cases in young toddlers are brought on by trauma caused by improperly fitting shoes or excessive thumb sucking. Dermatologists usually diagnose the condition by placing a drop of water on the nail plate. Treatment mostly depends on managing the underlying cause. Foods rich in iron such as beans and lentils, dark chocolate, fish, and spinach are the mainstay of treatment for koilonychia in children. Moreover, koilonychia can be an important predictor of underlying systemic conditions, including trichothiodystrophy, Darier disease, and LEOPARD syndrome.

Onychocryptosis

Onychocryptosis, most commonly known as ingrown toenails, is among the most frequently seen nail condition. It may cause extreme discomfort and hamper a child’s everyday activities.

Onychocryptosis is characterized by redness and swelling surrounding the nail folds of the toes. Advanced disease may include symptoms like seropurulent discharge, granulation tissue, and tissue hypertrophy. Affected individuals may experience trouble walking or be rendered immobile due to their pain intensity. Erythema, inflammation, or discharge around the nail edge are other potential complaints from patients.

Although the etiology of this condition is not clear, genetic susceptibility, trauma, tight-fitted shoes, and incorrectly trimmed toenails are some of the contributing factors. Other factors may include fungal infection, hyperhidrosis, and onychotillomania. Treatment is indicated in severe cases when the pain is affecting children’s daily activities. Patients are advised to reduce the risk of their children developing the condition by following tips such as having them wear comfortable shoes, treating underlying conditions, and asking for help trimming toenails.

Treatment can either be operative or nonoperative, depending on the patient’s condition. With nonoperative treatment, the patient’s toe is soaked in warm water for 10 minutes, followed by the application of antibiotic ointment twice a day. Operative options are indicated for patients who don’t respond to nonoperative treatment and may include complete or partial nail avulsion alone or in association with germinal matrix ablation.

Trachyonychia

Trachyonychia presents with longitudinally ridged nails, commonly known as opaque trachyonychia, or may manifest in a uniform, opalescent pattern with pits, known as shiny trachyonychia.

In most cases, a diagnosis of trachyonychia may be made based only on the patient’s clinical presentation. However, histologic examination of nail clipping to detect fungal infection is a legitimate element of examining onychodystrophy.

The matrix of nail unit samples taken for diagnosing trachyonychia typically displays a spongiotic pattern. A nail matrix specimen can be examined under a microscope to reveal histopathologic signs of the underlying disease, such as lichen planus or psoriasis, in cases of trachyonychia.

Improvements in trachyonychia have been recorded following intraläsional steroid injections at doses such as 2.5 to 3 mg/mL and 10 mg/mL. In children, it is advisable to start with a lesser concentration to prevent any localized adverse effects. Other topical treatments include topical steroids, tazarotene (Tazorac) 0.1% gel, topical psoralsen ultraviolet A (PUVA), and urea cream. Oral biotin and pulse-dosage oral steroids, such as 4 mg of betamethasone and low-dose acitretin (Soriatane), are some of the other effective treatments.

Onychomycosis

Onychomycosis is an infection caused by a fungus that invades the nail bed. The affected nail may have a thick, yellow appearance and become coarse or brittle. Onychomycosis tends to run in families; however, research suggests that it is more common in children with Down syndrome and immunodeficiencies and may pose a severe health problem in such patients.

Fungal nail infections may be diagnosed with a potassium hydroxide test, a fungal culture, or a histopathologic study of the nail plates. Dermoscopy, reflectance confocal microscopy, and artificial intelligence are just a few examples of the newer diagnostic tools that have been developed to enhance onychomycosis detection in the clinic, whereas mycological tools like molecular assays have been developed to better detect the fungus in the laboratory. Because the toenail grows so slowly, therapy can be difficult and a full recovery could take a year or more. Systemic antifungal medicines like itraconazole (Sporanox), terbinafine (Lamisil), and fluconazole (Diflucan) and topical antifungal drugs like efinaconazole (Jublia), ciclopirox, and tavaborole (Kerydin) are typically used in therapy. Children’s nails are thinner and grow more quickly than those of adults, so they often react better to topical antibiotics.

Beau Lines

Beau lines result from the decreased mitotic activity of keratinocytes in the proximal nail matrix, thinning the nail plate and causing transverse groove formation. The depth and width of the depression signify the degree of damage and duration of the insult, respectively. Damage, infection, or problems in the nail fold are all possible causes. Some other causative factors may include diabetes, hypocalcemia, and chemotherapeutic drugs. Postnatal onset is the norm; nevertheless, Beau lines may be observed in older children following a high fever or may be associated with zinc deficiency in rare cases. Beau lines in more than one nail may signify a systemic sickness, long-term exposure to a potentially harmful environment, or a chronic condition, and thicker lines might be due to long-term sickness or trauma exposure.
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4 out of 5 children were flare-free for 6 months when using Eucerin® Eczema Relief Cream\(^1\)

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pH-optimized regimen | Fortifies and protects skin barrier | Prevents and soothes flares

The Dx and Rx of Congenital Malalignment Syndrome in Children

Amar Davé, MD, FAAP; and Pahroul Davé, APN

Congenital malalignment syndrome or congenital malalignment of the great toes is a dystrophic nail disorder caused by the lateral rotation of the nail matrix. The malalignment results in altered growth of the nail plate that is not directed along the major axis of the distal phalanx.

Clinical appearance presents as lateral deviation of the nail plate, nail plate thickening, nail discoloration (brown, black, green-brown, yellow), transverse grooves across the nail, and frequently only involving the great toes.

Complications of the disorder include acute/chronic paronychia, onychogryphosis (hypertrophy of nail), onycholysis (detachment of the nail from bed), onychomadesis (shedding of a large portion of the nail), onychocryptosis (ingrown nail), hyperkeratosis (increased scaling of the nail bed), brachyonychia (short nail), and discoloration of the nail plate. Variations in the condition include medial deviation, the involvement of other toes and fingers, and single toe involvement.

The disorder is generally present at the time of birth. However, in individuals with minimal deviation, clinical manifestations may not be apparent until a child is older or when he or she begins to experience repetitive microtraumas or mechanical stress to the toenail from tight shoes, activities, and sports.

The etiology and pathogenesis of congenital malalignment are debated in the literature. Etiology is thought to be due to autosomal dominant genetic factors, extrinsic factors including constriction of toes by amniotic bands, increased intrauterine pressure, vascular abnormalities during fetal life, or a combination of genetically determined malalignment plus superimposed cumulative effects of postnatal trauma. Pathological features are discussed as increased tension of the extensor tendon of the hallux, and desynchronization in growth between the nail and the distal phalanges of the hallux, resulting in larger nail plates.

The treatment of congenital malalignment is based on the degree of deviation. Spontaneous improvement may occur in half patients before age 10 years. Conservative treatment in an individual with minimal deviation involves managing complications and wearing properly fitting, comfortable footwear. Severe deviations may call for surgery to align the nail matrix. The malalignment often appears on the thumbs and big toes of the pediatric population during the early years of life. In children, nail biting and thumb sucking are aggravating factors, but trauma is the primary cause.

Onychocchia

Onychocchia, also called lamellar dystrophy, is characterized by horizontal splits in the fingernails. It often coexists with onychorrhexis, which is longitudinal splits in the nail plate; collectively, they are referred to as bristle nail syndrome. Onychocchia usually appears on the thumbs and big toes of the pediatric population during the early years of life. In children, nail biting and thumb sucking are aggravating factors, but trauma is the primary cause.

Onychocchia necessitates a thorough examination of all 20 nail units. The nail plate, lunula, and proximal, distal, and lateral nail folds should all be examined carefully. It is vital to take note of any periungual scaling, erythema, or other cutaneous symptoms that may indicate an underlying dermatologic condition. Nail onycholysis and increased longitudinal or transverse nail curvatures should be evaluated. Abnormalities in the capillaries of the proximal nail folds may indicate an autoimmune connective-tissue illness; hence, a capillaroscopy of the nails should be conducted. The presence of ischemia and cyanosis indicates that poor circulatory flow may also contribute to the condition. Although treating onychocchia is challenging, a conservative management approach and/or oral supplements can aid in the healing process. Application of lotions containing α-hydroxy acids after soaking the nails in water for 5 minutes is among the best treatment strategies. Biotin has shown promising results when taken orally.

References

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The dermatologist might diagnose Beau lines after thoroughly examining the nails and reviewing the patient’s medical history. The thickness and number of lines may also indicate the cause. Unfortunately, there is no treatment for Beau lines, but treating the underlying cause may help improve the outcome.

Onycholysis

Onycholysis is a condition in which the nail bed separates from the nail plate, resulting in an opaque white appearance of the affected part. It is mainly caused by trauma, medications, or nail infections but is sometimes associated with autoimmune diseases. The condition may predispose to secondary nail infections, most commonly by Pseudomonas aeruginosa and Candida albicans.

Clinically, onycholysis can be diagnosed by taking a patient’s history and doing a physical exam to determine the root cause. If the root of the problem is unclear, an examination of all 20 nail units. The nail plate, lunula, and proximal, distal, and lateral nail folds should be evaluated. Abnormalities in the capillaries of the proximal nail folds may indicate an autoimmune connective-tissue illness; hence, a capillaroscopy of the nails should be conducted. The presence of ischemia and cyanosis indicates that poor circulatory flow may also contribute to the condition. Although treating onychoschizia is challenging, a conservative management approach and/or oral supplements can aid in the healing process. Application of lotions containing α-hydroxy acids after soaking the nails in water for 5 minutes is among the best treatment strategies. Biotin has shown promising results when taken orally.
A BIOSIMILAR IS NOT INTERCHANGEABLE unless the FDA says so.

To be designated an Interchangeable biosimilar by the FDA, an additional study is required.*

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*One or more studies may be required by the FDA to demonstrate Interchangeability.
Introducing ZORYVE, a next-generation topical PDE4i designed to simplify management of plaque psoriasis\(^1,3\)

The first and only topical PDE4i for plaque psoriasis—a once-daily cream without steroids for all affected areas of the body*\(^1,3\)

*Scalp excluded. Treatment of palms and soles excluded from efficacy analysis.

PDE4i = phosphodiesterase 4 inhibitor


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COM-ARQ-151-2100003 (v2.0) 08/2022
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See the data at zoryvehcp.com

The first and only topical PDE4i for plaque psoriasis—a once-daily cream without steroids for all affected areas of the body.*

*Scalp excluded. Treatment of palms and soles excluded from efficacy analysis.

PDE4i = phosphodiesterase 4 inhibitor

References:

Indication
ZORYVE is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.

Important Safety Information
The use of ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

The most common adverse reactions (≥1%) include diarrhea (3%), headache (2%), insomnia (1%), nausea (1%), application site pain (1%), upper respiratory tract infection (1%), and urinary tract infection (1%).

Please see brief summary of full Prescribing Information for ZORYVE on the following page.
Brief Summary of Prescribing Information for ZORYVE™ (roflumilast) cream, for topical use. See package insert for full Prescribing Information.

INDICATIONS AND USAGE ZORYVE is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.

DOSEAGE AND ADMINISTRATION Apply ZORYVE to affected areas once daily and rub in completely. Wash hands after application, unless ZORYVE is for treatment of the hands. ZORYVE is for topical use only and not for ophthalmic, oral, or intraocular use.

CONTRAINDICATIONS The use of ZORYVE is contraindicated in the following condition:
- Moderate to severe liver impairment (Child-Pugh B or C)

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 multicenter, randomized, double-blind, vehicle-controlled trials (DERMIS-1 and DERMIS-2), 881 subjects 2 years of age or older with plaque psoriasis were treated with ZORYVE or vehicle once daily for 8 weeks.

The median age was 47 years (range 6 to 88). The majority of the subjects were male (64%) and White (82%). The median body surface area (BSA) affected was 5.5% (range 2% to 25%).

The proportion of subjects who discontinued treatment due to adverse reaction was 1.0% for subjects treated with ZORYVE and 1.5% for subjects treated with vehicle. The most common adverse reactions that led to discontinuation of ZORYVE was application site urticaria (0.3%).

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ZORYVE, and for which the rate exceeded the rate for vehicle.

Table 1. Adverse Reactions Reported in ≥1% of Subjects Treated with ZORYVE for 8 Weeks

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZORYVE (N=576) n (%)</th>
<th>Vehicle (N=305) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>18 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (2.4)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (1.4)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>6 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (1.0)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

In 594 subjects who continued treatment with ZORYVE for up to 64 weeks in open-label extension trials, the adverse reaction profile was similar to that observed in vehicle-controlled trials.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no randomized clinical trials of oral or topical roflumilast in pregnant women. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 9 and 8 times the maximum recommended human dose (MRHD), respectively. Roflumilast induced post-implantation loss in rats at oral doses greater than or equal to 3 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 5 and 15 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 15 times the MRHD during pregnancy and lactation periods in mice.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations Labor and delivery ZORYVE should not be used during labor and delivery. There are no human studies that have investigated effects of ZORYVE on preterm labor or labor at term; however, animal studies showed that oral roflumilast disrupted the labor and delivery process in mice.

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m² basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m² basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (3 times the MRHD on a mg/m² basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (9 times the MRHD on a mg/m² basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 0.8 mg/kg/day (8 times the MRHD on a mg/m² basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (5 and 15 times the MRHD on a mg/m² basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (5 times the MRHD on a mg/m² basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (15 times the MRHD on a mg/m² basis). Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (29 times the MRHD on a mg/m² basis).

Lactation

Risk Summary There is no information regarding the presence of ZORYVE in human milk, the effects of ZORYVE on the breastfed infant, or the effects on milk production.

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. When a drug is present in human milk, it is likely that the drug will present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZORYVE and any potential adverse effects on the breastfed infant from ZORYVE or from the underlying maternal condition.

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

Data

Animal data Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

Pediatric Use

The safety and effectiveness of ZORYVE have been established in pediatric patients ages 12 years and older for the treatment of plaque psoriasis. Use of ZORYVE in this age group is supported by data from two 8-week vehicle-controlled safety and efficacy trials with the breastfed infant, or the effects on milk production.

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Geriatric Use

Of the 881 subjects with psoriasis exposed to ZORYVE or vehicle for up to 8 weeks in 2 controlled clinical trials, 106 were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted.

Hepatic Impairment

Oral roflumilast 250 mcg once daily for 14 days was studied in subjects with hepatic impairment. The AUC and Cmax values of roflumilast and roflumilast N-oxide were increased in subjects with moderate (Child-Pugh B) hepatic impairment. ZORYVE is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).
A Close Look at Necrobiosis Lipoidica

How to diagnose and treat this rare skin disorder

Jazmin Newton, Staff Correspondent

Necrobiosis Lipoidica (NL), also referred to as necrobiotic lipodermatosclerosis, is a rare, inflammatory granulomatous disease, causing cutaneous collagen degeneration which increases the risk for ulceration of the skin, particularly after trauma. The disease is generally idiopathic, though it is traditionally associated with type 1 diabetes mellitus and cited to affect 0.3%-1.2% of pediatric diabetics. It classically presents as yellow-brown, atrophic, telangiectatic plaques with an elevated violaceous rim, classically on the pretibial surface. NL is typically chronic; most commonly occurring in women between the ages of 30 and 40 and is often associated with underlying autoimmune and inflammatory disorders. Skin biopsy revealing granulomatous inflammation, parallel collagen degeneration involving the entire dermis and extending into the subcutaneous fat, endothelial cell swelling, and thickening of the blood vessel walls should raise suspicion for this disease.

Clinical Presentation
Skin lesions begin as 1- to 3-mm, well-demarcated papules that expand to become red-brown plaques with indurated borders and waxy centers (Figure 1). They later evolve into larger yellow-brown, shiny, atrophic, telangiectatic plaques with a violaceous rim (Figure 2). Central epidermal atrophy of the plaques increases the risk for ulceration. Ulceration occurs in roughly one-third of lesions, usually following minor trauma. Trauma can also cause the appearance of new skin lesions on previously unaffected skin or Koeberner phenomenon. Lesions classically present on the pretibial surface, though lesions have been less commonly identified on the upper extremities, face, and scalp. The plaques are usually multiple and bilateral.

Etiology
The etiology of NL is largely unknown, though immune-mediated vascular disease is most widely accepted theory for the driver of this disorder. Common theories implicate immune complex deposition or microangiopathic changes as causes of vascular injury and subsequent collagen alteration. Still others attribute the development of NL to diabetic microangiopathy, immunoglobulins, complement, or fibrinogen deposition, abnormal collagen fibrils, impaired neutrophil migration, metabolic changes, or tumor necrosis factor-alpha. The tensile strength of collagen is depleted given the loss of the cross-striations of collagen fibrils. Defective neutrophil migration is a suspected cause of granuloma formation, as macrophages take on the neutrophil role and accumulate, with subsequent granuloma formation.

Risk Factors/Associated Disease
Though NL can occur in otherwise healthy individuals, there is an increased prevalence of disease among individuals with diabetes mellitus, particularly type 1. However, there is still debate regarding whether there is a relationship between glycemic control and risk of developing NL. Other comorbidities associated with NL include hypertension, hyperlipidemia, obesity, thyroid disorders, and inflammatory diseases, such as Crohn disease, ulcerative colitis, rheumatoid arthritis, and sarcoidosis.

Diagnosis
NL is primarily a clinical diagnosis; however, clinical suspicion often warrants a skin biopsy to rule out other similarly presenting diseases, mainly granuloma annulare, necrobiotic xanthogranuloma, sarcoidosis, diabetic dermopathy, and Lipodermatosclerosis (Table). Further, given its association with diabetes, obtaining baseline blood work including fasting blood glucose or glycosylated hemoglobin has become relatively standard.

Histopathology
Histopathology reveals a normal or atrophic epidermis, with scattered palisaded and interstitial granulomatous dermatitis with layered tiers of granulomatous inflammation parallel to the skin surface, mixed with patches of collagen degeneration involving the entire dermis and extending into the subcutaneous fat septae. Endothelial cells characteristically reveal swelling and thickening of the blood vessel walls from the middle to deep dermis, which can also be found in diabetic microangiopathy.

Management/Treatment
There is currently no standard treatment guideline for patients diagnosed with NL and it is rather
difficult to treat. For early-stage lesions, first-line therapy typically includes potent topical corticosteroids. Established lesions may benefit from intralesional corticosteroids injection into the active borders. For inactive, atrophic lesions, topical steroids should be avoided as they may exacerbate the atrophy and increase risk of ulceration. When ulcerations are present, proper wound care principles are important. UV light therapy, lasers, TNF-alpha inhibitors, calcineurin inhibitors, biologics, platelet inhibitors, surgery, and more recently JAK-inhibitors have also been trialed as treatment options for NL with varying results. Treatment may provide intermittent disease quiescence, but since chronic in nature, it shows variable progression. Sites of previous ulceration or trauma are more susceptible to progressing to squamous cell carcinoma, and though this has been rarely reported, some argue for annual monitoring for transition to cancer following diagnosis. Ulcers can be painful, require extensive wound care, become infected, heal with scarring, and overall can significantly increase morbidity. Those with edema and associated venous disease of lymphedema may find compression therapy beneficial as adjunct treatment.

Table. Comparison of Clinical Presentation and Underlying Associated Diseases for Necrobiosis Lipoidica and its Differential Diagnoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Presentation</th>
<th>Associated Underlying Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrobiosis lipoidica</td>
<td>Asymptomatic yellow-brown to red-brown papules or nodules, that evolve into yellow-brown-atrophic plaques with an elevated violaceous border</td>
<td>Type I diabetes mellitus, sarcoidosis, inflammatory bowel disease, autoimmune thyroiditis, monochonal gammapathies</td>
</tr>
<tr>
<td>Granuloma annulare</td>
<td>Annular or arcuate red to brown papules or plaques without scale</td>
<td>Diabetes mellitus, thyroid disorders, dyslipidemia, malignancy, infection</td>
</tr>
<tr>
<td>Necrobiosis xanthogranuloma</td>
<td>Firm yellow to orange papules, plaques, and nodules, +/- erythematous border, telangiectasias, and atrophic center. Most commonly in peribulbar region.</td>
<td>IgG monoclonal gammapathy, multiple myeloma, monoclonal gammapathy of undetermined significance</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Red-brown macules and papules seen on extensor surfaces; firm, oval, flesh-colored, or violaceous subcutaneous nodules may be present on the trunk or the extremities (Darier-Roussy variant); widespread macules or papules with scale that may coalesce, ranging in color from yellow-brown to red-brown;</td>
<td>Bilateral hilar and mediastinal lymphadenopathy, lung parenchymal infiltrates, pulmonary fibrosis, arthritis, uveitis, erythema nodosum (rare in children)</td>
</tr>
<tr>
<td>Diabetic dermopathy</td>
<td>Shins with red to brown macules, patches, and papules +/- atrophy and scale</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Lipodermatosclerosis</td>
<td>Localized, very tender and painful erythematous, hyperpigmented indurated plaque on the lower legs</td>
<td>Venous insufficiency, obesity, hypercoagulable disorders, varicose veins, history of deep vein thrombosis</td>
</tr>
</tbody>
</table>

References
Help accelerate healing with a:

- Unique blend of 41% petrolatum (skin protectant), barrier lipids, humectants, and skin conditioners
- Protective, breathable barrier
- Moisture regulator that also allows the inflow of oxygen

See how Aquaphor Healing Ointment® helps healing
The Psychosocial Impact of Skin Diseases in Children

Acne, molluscum, atopic dermatitis, and other dermatological disorders can be detrimental to quality of life for children and their families.

Muhammad Aamir Anees and Bernard A. Cohen, MD, Staff Correspondents

Pediatric dermatology involves not only treating patients’ skin but also managing the psychosocial impact a disease has on children and their families, which can be significant. Many skin conditions have a quality-of-life (QOL) effect similar to that of systemic diseases such as renal disease, cystic fibrosis, and asthma. Skin diseases also can have emotional and social repercussions on the parents and caregivers of children with dermatological disorders. For clinicians to provide optimal patient care, family support is essential.

The widely used Children’s Dermatology Life Quality Index (CDLQI), which was developed in 1995, gives the practitioner an understanding of QOL issues in children aged 4 to 16 years. The latest cartoon version is easier and faster for children to complete and was shown to have a score similar to the original scale. The questionnaire, which uses a recall period of 1 week, assesses various issues including feelings of sadness or self-consciousness, impact on friendships, bullying as a result of the disease, effects on going out or playing sports, interference with sleep, and response to treatment. Based on the scoring of the responses, the effect on QOL is stratified as none (0-1), small (2-6), moderate (7-12), very large (13-18), or extremely large (19-20). Findings from a 2016 meta-analysis of all studies using CDLQI, which included data from 7,798 children with more than 20 conditions, concluded that most skin diseases have a major impact on QOL in a small proportion of children. However, further review of the literature demonstrates that skin disease has a significant impact for many children and their families.

Disease-specific scoring systems have also been developed, such as the the Cardiff Acne Disability Index, the Psoriasis Area Severity Index (PASI) and Physician Global Assessment, the Infants’ Dermatology Quality of Life, the Childhood Atopic Dermatitis Impact Scale, the Quality of Life Index for Atopic Dermatitis, and Dermatitis Family Impact questionnaire. These scoring systems not only help with assessing severity of disease but also give insight into QOL issues that are important for physicians to address.

This brief review discusses the QOL impact of a number of skin conditions compared with other chronic systemic diseases.

Psoriasis
Psoriasis is a chronic inflammatory disease of autoimmune etiology that is not completely curable. Seen in an estimated 0.7% of children, psoriasis has a negative impact on QOL for not only children but also their parents and caregivers, even in the presence of mild disease. Results show that 36% of parents and caregivers of children with psoriasis have anxiety and depressive symptoms.

Compared with systemic diseases using the corresponding Children’s Life Quality Index (CLQI), psoriasis was found to have a greater impact in QOL compared with enuresis, diabetes, and epilepsy. Psoriasis was also found to have a negative influence on physical activity, self-esteem, bullying, and stigmatization.

Investigators of another study concluded that improvement in CDLQI scores to imply no effect (0-1) was associated with a PASI score of > 90%, a decrease in body surface area (BSA) involvement. As a consequence, this may be advised as a reasonable therapeutic goal. It was also noted that systemic therapy including biological and conventional drugs has a better outcome compared with topical agents.

Thus, physicians are advised to follow a combined approach including clinical therapy and QOL assessment to evaluate improvement or impairment, family counseling, and support.

Atopic Dermatitis
With an estimated increasing global prevalence of 15.5% to 20% among children, atopic dermatitis (AD) is a chronic skin disease with relapses and remissions characterized by a wide array of clinical presentations that vary with age, environmental triggers, and genetic predisposition. The impact on QOL was found to be greater in children with AD compared with children with systemic diseases including renal disease, cystic fibrosis, asthma, and chronic urticaria. AD commonly arises in early childhood, with hallmark pruritic lesions that often worsen at night. Those with active AD alone had nearly 50% greater odds of reporting sleep-quality disturbances throughout childhood compared with 80% of children who also had asthma and/or allergic rhinitis. Consequently, early diagnosis and therapeutic interventions are needed to address QOL issues.

Recent findings also revealed a relative risk of 1.4 for learning disabilities among children with AD, an association independent of sociodemographic factors and other atopic and neurodevelopmental disorders. Significant positive association of atopic disease, and childhood AD with memory impairment, developmental delay, and cognitive dysfunctions has also been identified.

Acne
With a global prevalence of 9.38% and as one of the most common skin conditions among adolescents (findings reveal prevalence from 35% to close to 100%), acne vulgaris is rightly
described this way by Sulzeberger and Zaidens: “There is probably no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feeling of inferiority and greater sums of psychic suffering than does acne vulgaris.”

Acne profoundly affects self-perception, socialization, emotional health, and occupational opportunities as well as body dissatisfaction. The point estimate from 5 studies using the CDLQI to assess QOL in children with acne is 5.3; that corresponds to a small effect size.

For full list of references, visit dermatologytimes.com
**INDICATION**

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

**Limitations of Use:** SOTYKTU is not recommended for use in combination with other potent immunosuppressants.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

SOTYKTU is contraindicated in patients with a history of hypersensitivity reaction to deucravacitinib or to any of the excipients in SOTYKTU.

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity:** Hypersensitivity reactions such as angioedema have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SOTYKTU.

Please see additional Important Safety Information and Brief Summary of U.S. Full Prescribing Information for SOTYKTU on the following pages.

*TYK2 is a member of the Janus kinase (JAK) family.*
**TYK2** is a member of the Janus kinase (JAK) family.

Please see additional Important Safety Information and Brief Summary of U.S. Full Prescribing Information

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

**STUDY RESULTS**

*POETYK PSO-1 (N=664) and POETYK PSO-2 (N=1020) were two, 52-week, multicenter randomized, double-blind, placebo- and active (apremilast) 30 mg twice daily-controlled, Phase 3 studies to evaluate the safety and efficacy of SOTYKTU (6 mg once daily) in adult patients with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Patients had a body surface area (BSA) involvement of ≥10%, a Psoriasis Area and Severity Index (PASI) score ≥12, and a static Physician’s Global Assessment (sPGA) ≥3 (moderate or severe).

Both studies assessed the responders at Week 16 compared with placebo for the two co-primary endpoints:

- The proportion of patients who achieved at least a 75% improvement in PASI scores from baseline (PASI 75)
- The proportion of patients who achieved an sPGA score of 0 (clear) or 1 (almost clear)

There were multiple ranked secondary endpoints, including:

- The proportion of patients who achieved PASI 75 at Week 16 vs apremilast

**SELECT IMPORTANT SAFETY INFORMATION**

In the POETYK PSO-1 and POETYK PSO-2 trials, through Week 16, the most common adverse reactions (≥1% and higher than placebo) in patients taking SOTYKTU (n=840) were upper respiratory infections (9.2%), blood creatine phosphokinase increase (2.7%), herpes simplex (2.0%), mouth ulcers (1.9%), folliculitis (1.7%), and acne (1.4%).

BSA=body surface area; PASI=psoriasis area and severity index; PASI 75=75% reduction from baseline in PASI; PASI 90=90% reduction from baseline in PASI; PSSD=Psoriasis Symptoms and Signs Diary; sPGA=static Physician’s Global Assessment; ss-PGA=scalp-specific Physician’s Global Assessment; TYK2=tyrosine kinase 2.

Otezla® is a registered trademark of Amgen, Inc. SOTYKTU tablet is not actual size. Shown for illustrative purposes only.
SOTYKTU (deucravacitinib) INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION
SOTYKTU™ (deucravacitinib) is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Limitations of Use: SOTYKTU is not recommended for use in combination with other potent immunosuppressants.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
SOTYKTU is contraindicated in patients with a history of hypersensitivity reaction to deucravacitinib or to any of the excipients in SOTYKTU.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions such as angioedema have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SOTYKTU.

Infections: SOTYKTU may increase the risk of infections. Serious infections have been reported in patients with psoriasis who received SOTYKTU. The most common serious infections reported with SOTYKTU included pneumonia and COVID-19. Avoid use of SOTYKTU in patients with an active or serious infection. Consider the risks and benefits of treatment prior to initiating SOTYKTU in patients:
- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- 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. A patient who develops a new infection during treatment should undergo prompt and complete diagnostic testing, have appropriate antimicrobial therapy initiated and be closely monitored. Interrupt SOTYKTU if a patient develops a serious infection. Do not resume SOTYKTU until the infection resolves or is adequately treated.

Viral Reactivation
Herpes virus reactivation (e.g., herpes zoster, herpes simplex) was reported in clinical trials with SOTYKTU. Through Week 16, herpes simplex infections were reported in 17 patients (6.8 per 100 patient-years) treated with SOTYKTU, and 1 patient (0.8 per 100 patient-years) treated with placebo. Multidermatomal herpes zoster was reported in an immunocompetent patient. During PSO-1, PSO-2, and the open-label extension trial, the majority of patients who reported events of herpes zoster while receiving SOTYKTU were under 50 years of age. The impact of SOTYKTU on chronic viral hepatitis reactivation is unknown. Consider viral hepatitis screening and monitoring for reactivation in accordance with clinical guidelines before starting and during therapy with SOTYKTU. If signs of reactivation occur, consult a hepatitis specialist. SOTYKTU is not recommended for use in patients with active hepatitis B or hepatitis C.

Tuberculosis (TB): In clinical trials, of 4 patients with latent TB who were treated with SOTYKTU and received appropriate TB prophylaxis, no patients developed active TB (during the mean follow-up of 34 weeks). One patient, who did not have latent TB, developed active TB after receiving 54 weeks of SOTYKTU. Evaluate patients for latent and active TB infection prior to initiating treatment with SOTYKTU. Do not administer SOTYKTU to patients with active TB. Initiate treatment of latent TB prior to administering SOTYKTU. Consider anti-TB therapy prior to initiation of SOTYKTU in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during treatment.

Malignancy including Lymphomas: Malignancies, including lymphomas, were observed in clinical trials with SOTYKTU. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with SOTYKTU, particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer) and patients who develop a malignancy when on treatment with SOTYKTU.
**Rhabdomyolysis and Elevated CPK:** Treatment with SOTYKTU was associated with an increased incidence of asymptomatic creatine phosphokinase (CPK) elevation and rhabdomyolysis compared to placebo. Discontinue SOTYKTU if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

**Laboratory Abnormalities:** Treatment with SOTYKTU was associated with increases in triglyceride levels. Periodically evaluate serum triglycerides according to clinical guidelines during treatment. SOTYKTU treatment was associated with an increase in the incidence of liver enzyme elevation compared to placebo. Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease according to routine management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt SOTYKTU until a diagnosis of liver injury is excluded.

**Immunizations:** Prior to initiating therapy with SOTYKTU, consider completion of all age-appropriate immunizations according to current immunization guidelines including prophylactic herpes zoster vaccination. Avoid use of live vaccines in patients treated with SOTYKTU. The response to live or non-live vaccines has not been evaluated.

**Potential Risks Related to JAK Inhibition:** It is not known whether tyrosine kinase 2 (TYK2) inhibition may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition. In a large, randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA), patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. SOTYKTU is not approved for use in RA.

**ADVERSE REACTIONS**

Most common adverse reactions (≥1% of patients on SOTYKTU and more frequently than with placebo) include upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis and acne.

**SPECIFIC POPULATIONS**

**Pregnancy:** Available data from case reports on SOTYKTU use during pregnancy are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Report pregnancies to the Bristol-Myers Squibb Company’s Adverse Event reporting line at 1-800-721-5072.

**Lactation:** There are no data on the presence of SOTYKTU in human milk, the effects on the breastfed infant, or the effects on milk production. SOTYKTU is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SOTYKTU and any potential adverse effects on the breastfed infant from SOTYKTU or from the underlying maternal condition.

**Hepatic Impairment:** SOTYKTU is not available in 6 mg tablets.

SOTYKTU is available in 6 mg tablets.

**Please see Brief Summary of U.S. Full Prescribing Information, including Medication Guide, for SOTYKTU on the following pages.**

**References:**

Immunizations
Prior to initiating therapy with SOTYKTU (deucravacitinib), consider completion of all age-appropriate immunizations according to current immunization guidelines including prophylactic herpes zoster vaccination. Avoid use of live vaccines in patients treated with SOTYKTU. The response to live or non-live vaccines has not been evaluated.

Potential Risks Related to JAK Inhibition
It is not known whether TKY kinase may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition. In a large, randomized, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA), patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, including sudden cardiac death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with the JAK inhibition compared to those treated with TNF blockers. SOTYKTU is not approved for use in RA.

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

• Infections [see Warnings and Precautions]
• Malnourishing infections [see Warnings and Precautions]
• Laboratory Abnormalities [see Warnings and Precautions]

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.

The safety of SOTYKTU was evaluated in two placebo- and active-controlled trials (PSO-1 and PSO-2) and an open-label extension trial in which subjects who completed PSO-1 or PSO-2 could enroll (see Clinical Studies [14] in Full Prescribing Information). In these clinical trials, a total of 1,519 subjects with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy received SOTYKTU 6 mg orally once daily. Of these, 1,141 subjects were evaluated for safety for at least one year. In trials PSO-1 and PSO-2, 1,681 subjects were randomized to receive SOTYKTU 6 mg (840 subjects), placebo (419 subjects), or amlexanox 30 mg twice daily (422 subjects). All subjects randomized to placebo switched to SOTYKTU at Week 16. All other subjects remained in their original treatment group until Week 24, at which point subjects could have continued on the same treatment or be switched to SOTYKTU or placebo. The mean age of subjects was 47 years. The majority of subjects were White (87%) and male (67%).

In the 16-week placebo-controlled period of the pooled clinical trials (PSO-1 and PSO-2), discontinuation of therapy due to adverse reactions in subjects who received SOTYKTU was 4.4%, compared to 3.8% for placebo.

Table 1: Adverse Reactions that Occurred in ≥1% of Subjects with Plaque Psoriasis in the SOTYKTU Group and More Frequently than in the Placebo Group in Trials PSO-1 and PSO-2 through Week 16

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SOTYKTU N=1,141</th>
<th>Placebo N=419</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infectionsa</td>
<td>161 (14.2)</td>
<td>62 (14.8)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>23 (2.1)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>17 (1.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>16 (1.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>14 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Acnè</td>
<td>12 (1.1)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

* Includes upper respiratory tract infection (viral, bacterial, and unspecified), nasopharyngitis, pharyngitis (including viral, streptococcal, and unspecified), sinusitis (includes acute, viral, bacterial, rhinitis, rhinosinusitis, tracheitis, laryngitis, and tonsillitis, including bacterial, streptococcal).
* Includes oral herpes, genital herpes, herpes simplex, and herpes virus infection.
* Includes mouth ulceration, aphthous ulcer, tongue ulceration, and stomatitis.
* Includes acne, acne vulgaris, and dermatologic acne.

Adverse reactions that occurred in <1% of subjects in the SOTYKTU group were herpes zoster.

Specific Adverse Reactions
Exposure adjusted incidence rates are reported for all the adverse reactions presented below.

Infections
In the 16-week placebo-controlled period, infections occurred in 29% of the SOTYKTU group (116 events per 100 patient-years) compared to 32% of the placebo group (137 events per 100 patient-years). The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of SOTYKTU.

In the 16-week placebo-controlled period, serious infections were reported in 5 subjects (2.0 per 100 patient-years) treated with SOTYKTU and 2 subjects (1.0 per 100 patient-years) treated with placebo.

The most common serious infections reported during the 52-week treatment period were pneumonia and COVID-19.

Malignancies
During the 0-to-52-week treatment period of the two clinical trials, PSO-1 and PSO-2 (total exposure of 986 patient-years with SOTYKTU, malignancies (excluding non-melanoma skin cancer) were reported in 3 subjects treated with SOTYKTU (0.3 per 100 patient-years), including single cases each of breast cancer, hematopoietic carcinoma, and lymphoma after 24, 32, and 52 weeks of treatment, respectively.

During PSO-1, PSO-2, and the open-label extension trial in which subjects who completed the controlled trials could enroll, a total of 3 subjects (0.1 per 100 patient-years) developed lymphoma while receiving SOTYKTU after 25, 77, and 98 weeks of treatment.

Laboratory Abnormalities
Creatine Phosphokinase (CPK)
In the 16-week placebo-controlled period, increased CPK (including Grade 4) was reported in 22 subjects (9.3 per 100 patient-years) treated with SOTYKTU, and 5 subjects (4.1 per 100 patient-years) treated with placebo.

Liver Enzyme Elevations
Events of increases in liver enzymes ≥3 times the ULN were observed in subjects treated with SOTYKTU [see Warnings and Precautions]. In the 16-week placebo-controlled period:

• ALT elevations ≥3 times the ULN were reported in 9 subjects (0.6 per 100 patient-years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.
• AST elevations ≥3 times the ULN were reported in 13 subjects (5.2 per 100 patient-years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.

Decreased Glomerular Filtration Rate (GFR)
In the 16-week placebo-controlled period in subjects who had moderate renal impairment (eGFR 30-59 mL/min) at baseline, decreased GFR was reported in 4 subjects (1.6 per 100 patient-years) treated with SOTYKTU, and 1 subject (0.8 per 100 patient-years) treated with placebo. Two of the deucravacitinib-treated subjects had worsening of baseline proteinuria.
**OVERDOSAGE**

There is no experience regarding human overdosage with SOTYKTU (deucravacitinib). In case of overdose, contact the Poison Help line (1-800-222-1222) for additional overdosage management recommendations. The extent of deucravacitinib elimination by hemodialysis was small (5.4% of dose per dialysis treatment), and thus hemodialysis for treatment of overdose with SOTYKTU is limited.

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of deucravacitinib was assessed in 2-year rat and 6-month rasset2 transgenic mouse studies. No evidence of tumorigenesis was observed in male or female rats that received deucravacitinib at oral doses up to 15 mg/kg/day (51 times the MRHD based on AUC comparison). No evidence of tumorigenesis was observed in male or female Tg.rasH2 mice that received deucravacitinb at oral doses up to 60 mg/kg/day.

Deucravacitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an in vitro chromosomal aberration assay (cultured Chinese hamster ovary cells) or in an in vivo rat peripheral blood micronucleus assay.

In male rats, deucravacitinib had no effects on reproductive parameters (matings, fertility, and sperm morphology) or early embryonic development of their offspring at oral doses up to 50 mg/kg/day (224 times the MRHD based on AUC comparison).

In female rats, deucravacitinib had no effects on mating, fertility, or early embryonic parameters at oral doses up to 50 mg/kg/day (171 times the MRHD based on AUC comparison).

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide) before starting SOTYKTU therapy and each time the prescription is renewed, as there may be new information they need to know. Advise patients of the potential benefits and risks of SOTYKTU.

**Hypersensitivity Reactions**

Advise patients to discontinue SOTYKTU and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [see Warnings and Precautions].

**Infections**

Inform patients that SOTYKTU may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection [see Warnings and Precautions].

Inform patients that herpes infections, including serious, may occur with use of SOTYKTU. [see Warnings and Precautions].

**Malignancies Including Lymphomas**

Inform patients that SOTYKTU may increase their risk of developing malignancies including lymphomas. Instruct patients to inform their healthcare provider if they have ever had any type of cancer [see Warnings and Precautions].

**Rhabdomyolysis**

Inform patients that SOTYKTU may increase their risk of developing rhabdomyolysis. Instruct patients to immediately inform their healthcare provider if they develop unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever [see Warnings and Precautions].

**Laboratory Abnormalities**

Inform patients that SOTYKTU may affect certain lab tests, and that blood tests may be required before and during SOTYKTU treatment [see Warnings and Precautions].

**Immunizations**

Advise patients that vaccination with live vaccines is not recommended during SOTYKTU treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SOTYKTU prior to a potential vaccination [see Warnings and Precautions].

**Pregnancy**

Advise patients to report their pregnancy to Bristol-Myers Squibb Company at 1-800-721-5072 [see Use in Specific Populations].

**Manufactured by**

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3 Things You Should Know About Managing Alopecia Areata

Alopecia areata (AA) is a chronic autoimmune condition that damages the hair follicles. It typically presents with sharply defined round patches of nonscarring hair loss on the scalp. However, it can also affect the eyebrows, lashes, facial hair, and nails, and it can progress to alopecia totalis (total scalp hair loss) or alopecia universalis (total body hair loss). AA can have devastating effects on patients, but a greater understanding of its pathophysiology has led to the development of new treatment options.

Here are 3 things you should know about managing alopecia areata.

1. **AA can have a profound psychosocial impact.**

   With a lifetime incidence risk of approximately 2%, AA is the second most common cause of hair loss, behind androgenetic alopecia, and it affects men and women comparably.1-4 Up to 88% of patients experience their initial episode of AA prior to age 40 years, with spontaneous remission rates between 30% and 50% within the first 6 to 12 months of onset.5,6 Overall, the incidence of relapse is 85% and approaches 100% over 20 years.

   Patients with AA have a higher prevalence of depression, anxiety, and sleep problems than the general population.7,8 In a cross-sectional online survey study, 62% of patients said AA caused them to make different major life decisions with respect to relationships, education, or career. Additionally, 85% said that it is a daily challenge to cope with AA, and 47% reported anxiety and/or depression.9 Results of a systematic review showed that patients with AA consistently exhibit poor health-related quality of life, similar to patients with other chronic dermatologic diseases, including atopic dermatitis and psoriasis.8

2. **The pathogenesis of AA is gaining new insights.**

   The normal human hair growth cycle consists of 3 phases: anagen (active hair/follicular growth), catagen (regression/follicular involution), and telogen (follicular rest and shedding).11 In AA, autoimmune-mediated damage to the hair follicle in the anagen phase leads to premature transition to the catagen and telogen phases and subsequently to loss of hair.

   The anagen hair follicle normally has immune privilege due to production of local immunosuppressants and downregulation of major histocompatibility complex class I proteins, among other factors.12 Breakdown of immune privilege of the hair follicle (resulting from genetic, environmental, and immunologic factors) is thought to be a key element in the pathophysiology of AA.13 With the collapse of immune privilege, autoreactive CD8-positive and natural killer (NK) group 2D-positive (NK2D+) T cells can attack follicular epithelial cells.14

   The concerns of stigma in patients with AA may not be unfounded. A survey of 2015 laypersons who were shown 3 images of the same person with varying amounts of hair found that 30% of respondents thought of those with severe hair loss as sick, and 27% viewed them as unattractive. Stigma increased as degree of hair loss increased.14
When these T cells bind to autoantigens at the follicle, they release the cytokine interferon-γ (IFN-γ), which is a key driver of AA pathogenesis. In response to IFN-γ, follicular epithelial cells then signal via the Janus kinase (JAK)/signal transducer and activator of transcription (JAK-STAT) pathway to upregulate cytokines, including interleukin (IL)-2 and IL-15. IL-2 and IL-15 are known drivers of cytototoxic T-cell activity. JAK-mediated production of IL-15 promotes further inflammation and T-cell activation, causing additional release of IFN-γ via JAK signaling in a positive feedback loop. These cytokines and chemokines further recruit CD4-positive T cells and natural killer cells to the hair follicle, leading to dystrophy.

### Table. Select JAK Inhibitors Studied for Use in Alopecia Areata

<table>
<thead>
<tr>
<th>NAME</th>
<th>ROUTE OF ADMINISTRATION</th>
<th>CLINICAL TRIAL NCT (TRIAL NAME; PHASE)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>Topical</td>
<td>NCT02553330 (phase 2)</td>
<td>Ruxolitinib had no significant effects on hair regrowth vs. vehicle.²⁶</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Oral</td>
<td>NCT03570749 (BRAVE-AA1; phase 2)</td>
<td>In both trials, significantly more patients treated with baricitinib achieved 20% or less scalp hair loss at 36 weeks vs placebo.²¹</td>
</tr>
<tr>
<td>Breocpitinib</td>
<td>Oral</td>
<td>NCT05070606 (phase 2)</td>
<td>Trial is recruiting.²²</td>
</tr>
<tr>
<td>Ritlecitinib</td>
<td>Oral</td>
<td>NCT03732807 (ALLE-GRO-2b/3; phase 2/3)</td>
<td>In ALLEGRO-LT, ritlecitinib achieved the primary efficacy end point of proportion of patients with 20% or less scalp hair loss at 6 months vs placebo.²⁰ The ALLEGRO-LT long-term study is underway.²⁰</td>
</tr>
</tbody>
</table>

### KEY REFERENCES


### CME POST TEST QUESTIONS

Which of the following is NOT involved in the pathophysiology of alopecia areata?

A. CD8+ T cells
B. Interferon alpha
C. Interleukin (IL)-2
D. IL-15

CME Provider Contact Information
Physicians’ Education Resource®, LLC
2 Clarke Drive, Suite 110, Cranbury, NJ 08512
Toll-Free: 888-949-0045 | Local: 609-378-3701 | info@gotoper.com

To learn more about this topic, including information on the treatment of patients with alopecia areata, go to www.gotoper.com/aad22iss-art
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