DIAGNOSTIC BIAS IN SKIN OF COLOR

Loren Kreuger, MD, talked with Dermatology Times® about her recent research on the disparities in clinical decision-making facing patients of color.

KATIE HOBBINS | Editor

Disparities in treating patients of color for dermatologic disorders extend beyond macro concerns such as accessibility and awareness to medical issues such as bias in clinical decision-making, according to research presented at the 18th Annual Skin of Color (SOC) Scientific Symposium held March 24, 2022, in Boston, Massachusetts.1

DIAGNOSTIC BIAS CONTINUES ON PAGE 50

FEATURING
Rosacea Awareness Month
Pipeline updates and perspectives

DermatologyTimes.com
An IL-23 inhibitor for adults with moderate to severe 
plaque psoriasis (Ps) and for adults with active psoriatic arthritis (PsA)¹

N O T H I N G  I S  E V E R Y T H I N G

Nothing less than the opportunity to reach for their treatment goals.

For your patients, that’s everything.

SKYRIZI GIVES YOUR PATIENTS THE OPPORTUNITY FOR...

DURABLE, RAPID & CLEAR SKIN

In Ps, most patients achieved co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16, including response 4 weeks after 1st dose. Most patients who achieved PASI 90 at Week 16 maintained it at Week 52.
PASI 100 was achieved by many patients at Week 16 and by a majority at Week 52.²

POWERFUL JOINT SYMPTOM RELIEF

In PsA, a majority of patients achieved the primary endpoint of ACR20 at Week 24, experiencing improvement in joint symptoms including patient-reported pain data.¹

IN 4 INJECTIONS A YEAR

Reliable quarterly dosing after 2 initiation doses at Weeks 0 and 4 (150 mg/dose) for Ps and PsA.¹

Safety data up to ~7 years in Ps clinical trials. Safety profile observed in PsA is generally consistent to Ps.¹²

UltIMMa-1 & 2 STUDY DESIGN¹,³

UltIMMa-1 (N=506) and ultIMMa-2 (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and 16, and every 12 weeks thereafter. Co-primary endpoints were PASI 90 and sPGA 0/1 vs placebo in each study (assessed by non-responder imputation).

KEEPsAKE-1 & 2 STUDY DESIGN⁴

KEEPsAKE-1 and KEEPsAKE-2 were phase 3, multicenter, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of SKYRIZI in adults with active PsA. KEEPsAKE-1 included patients who had an inadequate response or intolerance to at least 1 DMARD. KEEPsAKE-2 included patients who had an inadequate response or intolerance to biologic therapy and/or DMARDs. Patients were randomized to SKYRIZI 150 mg or placebo followed by SKYRIZI 150 mg at Week 28.

References: 1.


Learn more by visiting www.SkyriziHCP.com/dermatology
Co-primary endpoints were PASI 90 and sPGA 0/1 vs placebo in psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous controlled studies to evaluate the efficacy and safety of SKYRIZI phase 3, randomized, double-blind, placebo- and active- (N=506) and UltIMMa-1 (N=491) were replicate UltIMMa-1 & 2 STUDY DESIGN 1,3 Safety data up to ~7 years in Ps clinical trials. Safety profile observed in PsA is generally consistent to Ps. 1,2 plaque psoriasis (Ps) and for adults with active psoriatic arthritis (PsA) An IL-23 inhibitor for adults with moderate to severe RAPID & CLEAR SKIN DURABLE, majority at Week 52. 1 patients at Week 16 and by a PASI 100 16 maintained it at Week 52. who achieved at Week 24, ACR20 achieved the primary endpoint, a majority of patients followed by SKYRIZI 150 mg at Week 28. Patients were randomized to SKYRIZI 150 mg or placebo included patients who had an inadequate response or intolerance to at least 1 DMARD. KeepSake-1 & 2 STUDY DESIGN 1,3 included patients who had an inadequate response or intolerance to at least 1 DMARD. KeepSake-1 was phase 3, multicenter, placebo-controlled studies designed and KeepSake-2 were phase 3, randomized, double-blind, placebo- and active- (N=506) and UltIMMa-1 (N=491) were replicate UltIMMa-1 & 2 STUDY DESIGN 1,3 Safety data up to ~7 years in Ps clinical trials. Safety profile observed in PsA is generally consistent to Ps. 1,2 plaque psoriasis (Ps) and for adults with active psoriatic arthritis (PsA). Plaque Psoriasis: integrated analysis of clinical study data. Poster presented at: 30th European Academy of Dermatology and Venereology Congress; September 29-October 2, 2021; virtual. Psoriatic Arthritis: SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Psoriatic Arthritis: SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults. Important Safety Information 1 Hypersensitivity Reactions SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately. Infection SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves. Tuberculosis (TB) Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB. Administration of Vaccines Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines. Adverse Reactions Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections. In psoriatic arthritis phase 3 trials, the incidence of hepatic events was higher with SKYRIZI compared to placebo. SKYRIZI is available in a 150 mg/mL prefilled syringe and pen. Please see the Brief Summary of the Full Prescribing Information on the following page.
**Table 1. Adverse Drug Reactions Occurring in ≥1% of Subjects on SKYRIZI through Week 16**

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>SKYRIZI® (n=1208)</th>
<th>Placebo (n=1200)</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>1.5% (19)</td>
<td>1.0% (3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.5% (33)</td>
<td>1.0% (3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>3.5% (46)</td>
<td>2.0% (6)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1.5% (19)</td>
<td>2.0% (24)</td>
<td>0.0066</td>
</tr>
<tr>
<td>Rash</td>
<td>1.5% (19)</td>
<td>0.0% (0)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.0% (12)</td>
<td>0.0% (0)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.0% (12)</td>
<td>0.0% (0)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*Significance calculated using chi-square test.
News Just for You, 24-7

You might notice a new logo on the cover of this issue: Medical World News®. It represents our Medical World News® (MWN) channel. If you are not familiar with this 24-7 platform, I invite you to visit it soon as you have the chance: www.medicalworldnews.com.

Easy to navigate and now in its fifth season, this website dedicated to medical news offers viewers 6 shows:

- **Inside the Practice** highlights a unique, nonclinical aspect of a specialty—for example, a nonphysician’s observations on aesthetic procedures and what is on the horizon.
- **Deep Dive** offers an in-depth look of a high-impact topic, such as COVID-19 vaccines and JAK inhibitors for treating atopic dermatitis.
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Our cover story invites physicians to ask themselves some tough questions on bias. Ethically, a dermatologist may not consider themselves to be biased. But would they be equally likely to biopsy the same skin cancer lesion or inflammatory skin disorder in their White patients and patients of color? According to research by Loren Krueger, MD, Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia, the answer, sadly, is no. Sadder still is her point that the reasons behind disparities in clinical decision-making to biopsy may have more to do with lack of education/information than any underlying bias.

Progress is being made, certainly. More images are available to show how skin disorders present on darker phototypes, and many universities have expanded required coursework to include the study of how to diagnose, treat, and manage skin and hair disorders in patients of color. Continuing education offered through events such as the 18th Annual Skin of Color Scientific Symposium, held March 24, 2022, in Boston, Massachusetts, and most major conferences across the specialty are adding to the expertise of all physicians in the specialty. This issue also calls attention to April as Rosacea Awareness Month. As Richard Gallo, MD, PhD, chair of the Department of Dermatology at the University of California, San Diego, and a member of Dermatology Times® editorial advisory board, said in this exclusive interview, microbial probiotics or prebiotics, hormonal modulation, and protean inhibitors may provide next-generation options for this challenging-to-treat disorder. Whether through MWN’s global look at medical news or Dermatology Times® focus on the specialty, we want to keep this community informed and engaged—however, whenever, and wherever physicians want information.

Mike Hennessy Jr, the president and co-founder of MWN

**Publisher’s note**

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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.

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.
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\(^1\)

WELL-STUDIED SAFETY
Clinical trial experience in >9,000 patients since 2012 across 3 approved indications\(^1\)

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

EXCEPTIONAL ACCESS
Committed to AbbVie’s legacy of reliable access and patient services

ROBUST RESULTS
90% skin improvement (EASI 90) measured at Week 16\(^1\)

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.

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IMPORTANT SAFETY INFORMATION

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 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 all-cause 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 nonmelanoma 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. 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 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 decreases in 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
Please see Brief Summary of full Prescribing Information on the following pages of this advertisement.
Clinical Studies

Upper respiratory tract infection (URTI)* 9.5 13.5

Malignancy and Lymphoproliferative Disorders

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

In a large, randomized, placebo-controlled trial of patients with moderate-to-severe rheumatoid arthritis (RA) treated with the JAK inhibitor tofacitinib, malignancies (excluding non-melanoma skin cancer (NMSC)) were observed in patients treated with the JAK inhibitor compared to those treated with placebo. Patients with a history of malignancy, including melanoma skin cancer, lymphomas, and lung cancer, were excluded from the study. The overall incidence of malignancy observed in patients treated with tofacitinib was consistent with what would be expected based on the risk of malignancy in patients with RA. In the 2-year extension of the trial, the incidence of malignancy was similar to that observed in the 2-year randomized portion of the trial. Sex, age, and smoking status are important risk factors for malignancy in patients with RA.

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In a large, randomized, placebo-controlled trial of patients with moderate-to-severe rheumatoid arthritis (RA) treated with the JAK inhibitor tofacitinib, malignancies (excluding non-melanoma skin cancer (NMSC)) were observed in patients treated with the JAK inhibitor compared to those treated with placebo. Patients with a history of malignancy, including melanoma skin cancer, lymphomas, and lung cancer, were excluded from the study. The overall incidence of malignancy observed in patients treated with tofacitinib was consistent with what would be expected based on the risk of malignancy in patients with RA. In the 2-year extension of the trial, the incidence of malignancy was similar to that observed in the 2-year randomized portion of the trial. Sex, age, and smoking status are important risk factors for malignancy in patients with RA.
**Clinical Considerations**

RINVOQ is contraindicated in patients with a history of severe hypersensitivity reaction to any component of RINVOQ, including potassium chloride.

**Warnings and Precautions**

**Herpes Zoster and Herpes Simplex Virus Infections**

Herpes zoster and herpes simplex virus infections are episodic conditions. Although the risk of initial herpes zoster infection is not increased in patients taking RINVOQ, the risk of recurrent herpes zoster or herpes simplex virus infections may be increased in patients taking RINVOQ.

**Cardiovascular Disease**

RINVOQ has not been studied in patients with cardiovascular disease. RINVOQ may increase the risk of major adverse cardiovascular events (MACE), including fatal and non-fatal myocardial infarction and fatal and non-fatal stroke.

**Immunization**

It is unknown whether immunization with live vaccines is safe in patients taking RINVOQ. It is recommended that patients receive a live vaccine at least 14 days before starting RINVOQ.

**Pediatric Use**

RINVOQ has not been studied in pediatric patients. No dosage adjustment is recommended for use in this population.

**Renal Impairment**

For patients with moderate (CrCL 30 to 60 mL/min) or severe renal impairment (CrCL <30 mL/min), no dosage adjustment is needed in patients with mild or moderate renal impairment.

**Pregnancy**

Pregnancy testing should be performed while using RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of an infection or if they develop a rash or fever.

**Breastfeeding**

RINVOQ is excreted in human milk. Advise female patients of reproductive potential to not breastfeed during treatment with RINVOQ.

**Lactation**

RINVOQ is contraindicated in patients with a history of severe hypersensitivity reaction to any component of RINVOQ, including potassium chloride.

**Drug Interactions**

RINVOQ is a potent inhibitor of CYP3A4. Concomitant administration of a strong CYP3A4 inhibitor with RINVOQ may result in increased exposure to RINVOQ and should be avoided.

**Adverse Reactions**

Most adverse reactions that occur in patients taking RINVOQ and RINVOQ monotherapy are mild to moderate in severity.

**Adverse Events**

The most common adverse reactions that occurred in patients taking RINVOQ in clinical trials were nasopharyngitis, upper respiratory tract infection, oral herpes, tonsillitis, upper respiratory tract infection, acute sinusitis, viral pharyngitis, staphylococcal pharyngitis, upper respiratory tract infection, streptococcal pharyngitis, sinusitis, rhinitis, tonsillitis, and nasopharyngitis.

**How To Give**

RINVOQ Tablets are available in 15 mg and 30 mg of upadacitinib.

**Dosage and Administration**

Administer RINVOQ tablets once daily with or without food. Do not split, chew, or open the tablets.

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# Medical World News

## REPORTS ON NUTRITION PLANS, THE SCIENCE BEHIND BURN WOUNDS, AND AESTHETIC TRENDS

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### Identifying Diagnostic Bias in Skin of Color

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Dermatologists must disseminate accurate information to their communities.

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Surgery remains the preferred treatment for pincer nails.

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Diverse Perspectives in Medical Aesthetics Matter More Than Ever

Terri L. Phillips, MD, FAAP

Evolution of Consumer Attitudes
Consumer attitudes about beauty and aging are driving rapid changes in the medical aesthetics industry. The COVID-19 pandemic has contributed significantly to a surge in demand, leading to more widespread acceptance and awareness of elective procedures. The American Academy of Facial Plastic and Reconstructive Surgery estimates that impacts of the pandemic have led to a 10% increase in cosmetic surgery, pointing to the “Zoom effect” and increased disposable income as major contributing factors in changing consumer behaviors. Further, self-care has become normalized—even an indicator of pride and confidence. With minimally invasive procedures increasingly incorporated into everyday beauty routines, aesthetics is no longer viewed as a luxury for a small demographic.

This increased demand positions the global medical aesthetics market to grow by 12% to 14% annually over the next 5 years. As the industry continues to advance with the next generation of products and procedures, dermatologists and aesthetic physicians also must adjust to meet the evolving and diverse needs of a growing patient population that includes people of all racial, ethnic, socioeconomic, gender, and age groups.

Recognizing the Needs, Goals of a Diverse Patient Base
More than 15.5 million cosmetic procedures were performed in 2020. Of that total, the American Society of Plastic Surgeons’ 2020 Plastic Surgery Statistics Report estimates that 86% were minimally invasive. The findings also show that in 2020, 1.78 million Black Americans opted for cosmetic procedures, a number rising annually from 1.68 million in 2018 and 1.77 million in 2019. Meanwhile, the medical aesthetics industry has done little to understand the unique aesthetic needs and desires of Black Americans. Treatment of facial aging patterns among White patients is well-documented, but there is far less information on how facial injectables and dermal fillers affect Black skin.

Perceptions that ethnic minorities do not have the same aesthetic concerns or means to address them continue. Narrow definitions of beauty do not necessarily reflect ethnic and aesthetic preferences of diverse populations around the world.

Recently, an advisory board of 10 leading dermatologists and aesthetic physicians from across the globe used a modified version of the Delphi method to establish a strong consensus on good skin quality. Members accessed an online platform to review peers’ statements on skin quality criteria, including treatment and measurement options, and voted to indicate whether they agreed or disagreed.

These can be described across all ethnicities, age groups, and genders by emergent perceptual categories related to skin: tone evenness, surface evenness, firmness, and glow.

These findings highlight the need for a more individualized approach to treatments that affect the skin—an integral part of one’s identity—and for broadening the scope of clinical trials to address the aesthetic concerns and treatment priorities of patients of all racial and ethnic backgrounds.

As individuals from a widening spectrum of age groups, socioeconomic, ethnic, and racial backgrounds seek medical aesthetic treatments to help them look and feel better, the industry must do a better job of keeping pace.

Making an Impact in Dermatology
Given the need to recognize important dermatologic conditions across a diverse patient base, educational resources have evolved to better equip health care professionals to meet the needs of patients with different skin types and ethnic backgrounds. Yet, while a younger, more diverse demographic is embracing noninvasive aesthetic treatments, the lack of health care providers and aesthetic professionals with the requisite background and training to understand the needs of people with different skin tones is disheartening.

Dermatology is one of the least diverse medical specialties. Black dermatologists make up just 3% of all dermatologists, an especially low proportion considering that more than 13% of the American population identify as Black or African American.

We need more providers who have experience and education in the special needs of skin of color, and that means training more people with diverse backgrounds as well as adjusting curricula for everyone entering the field. The next generation of providers must be equipped with the appropriate diagnostic and therapeutic tools to address the individual needs of patients seeking medical aesthetic interventions. To move away from the narrow viewpoints holding sway and build deeper respect for the preferences of diverse populations, medical training must expose practitioners to many points of view and a range of skin types, age groups, and ethnicities.

Taking Action Steps in Aesthetic Medicine
Our industry should widen its perspective on innovation and work diligently to foster inclusivity and gain a deeper understanding of where barriers and implicit bias exist in education and our offerings to patients. Collaborating with communities of color and promoting mentorship to bring a new, more diverse generation of health care providers into aesthetic medicine are of paramount importance as the constituency of the patient population expands.

Failure to solve these patients’ concerns would be a missed opportunity for all.

To encourage more people of color to pursue careers in medical aesthetics, more people of color, especially Black women, should be seen in leadership positions. Elevating individuals who recognize the value of diverse voices, inclusivity, and well-being as leaders will spark creativity, encourage unique thinking, and drive innovation within the field. Definitions of beauty need to evolve, and “normalizing” to a single standard based on a narrowly defined population must stop. It is past time to celebrate the unique features of the patients we serve and promote diversity in aesthetic medicine.

Looking Ahead
The aesthetic industry is specially poised to champion a diversity of patients and support the continued advancement and success of our industry. It is time to embrace the shifting consumer behaviors driving change and optimize the needs of all patients, delivering greater confidence to all who seek aesthetic treatments.

Disclosure
This study, “SkinQuality—A Holistic 360 View: Consensus Results,” was sponsored by Merz Aesthetics in Raleigh, North Carolina. Phillips is the chief medical dolls of skin of Merz Aesthetics.

For full list of references, see dermologytimes.com
The GentleMax Pro Plus™ system is the latest evolution in the #1 dermatologist-recommended brand for laser hair removal, built on a foundation of over 20 years of clinically proven performance across all skin types.¹

Learn how the GentleMax Pro Plus system can help grow your practice and your profits at 800-733-8550 or visit us at candelamedical.com/GMPP

¹. Proprietary Candela survey conducted by Wizer via Nielsen’s online physicians panel, 2015.
“Lactic acid is a key intermediate [molecule]. If you add more lactic acid to something, it drives the interaction backward.”
James Beckman, MD, Fayetteville, Arkansas

Aesthetics Insider

What is the science behind a skin burn, and how can better understanding lead to burn reversal? Can every physician achieve optimal wellness, and how can they tell whether their well routine is working? What arguments shape the ongoing controversy about nurse practitioners, physician assistants, and other allied health care workers performing in-office medical procedures such as injectables? Scan the QR codes or visit MJH Life Sciences® 24-hour Medical World News® (MWN) network to access more on these topics from the Dermatology Times® team.

LINDA STOCUM | Associate Editor

MWN is a platform where expert opinions and physician insights mix to bring the health care profession together in an innovative way. Check it out to take a deep dive into research, get a second opinion on complex cases, or go behind the science of game-changing breakthroughs. Listen in as colleagues reveal their after-hours talents, share how they take charge of their own well-being, and discuss what’s top of mind regarding their practices.

INSIDE THE PRACTICE: A NONPHYSICIAN’S POV
Shay Moinuddin, MHA, CANS, RN, an aesthetic nurse specialist who has been clinical manager at The Few Institute in Chicago, Illinois, since 2008 and manages day-to-day operations, talks with us about stackable aesthetic treatments, changes in the aesthetic world in the past 10 years, and ways allied health care workers should be used in the practice. Shay has had extensive training in injecting all brands of FDA-approved dermal fillers and neurotoxins and brings her perspective as a nonphysician injector to this discussion.

WELL-BEING CHECKUP: HYPERCUSTOMIZED NUTRITION STRATEGIES
Ben Schuff, ND, LDN, director of naturopathy and nutrition at BIÂN in Chicago, Illinois, drills down the details behind wellness. He explains how to develop a customized nutrition plan—a deeply individualized concept—and delves into why a nutrition plan must be personalized: There is no silver bullet, so each patient needs a program built around their physical, mental health, and lifestyle goals. He also discusses how to measure results of an intangible concept such as wellness when many people want metrics to monitor their progress. Schuff touches on subjects often forgotten in physicians’ day-to-day lives.

DEEP DIVE: THE BURN REVERSAL METHOD
James Beckman, MD, is a board-certified plastic surgeon and adjunct associate clinical professor in the Department of Dermatology at the University of Arkansas for Medical Sciences in Little Rock, as well as founder and CEO of Therapon Skin Health in Fayetteville, Arkansas. A biochemist, Beckman created a topical application that stops the progression of a first- or second-degree burn. He sits down to discuss the science with Dermatology Times® and explain this burn-reversal method, which uses lactic acid to stop burns in their tracks—an approach he began investigating in the 1990s. Beckman notes the complexities of working with burned skin, the discomfort that many health care professionals feel regarding treatment, and considerations when working with a patient with burns.

“As a provider in medicine, [I believe] the most important thing we can do for our patients is to be present with them, and to be present with them is to be mindful.”
Ben Schuff, ND, LDN, Chicago, Illinois
Cost of Copies Prompts a Lawsuit

**by DAVID J. GOLDBERG, MD, JD**

Goldberg is director of Skin Lasers and Surgery, Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mount Sinai; and adjunct professor of law at Fordham University School of Law, New York, New York.

Over the course of 12 years, Dr A, along with his associates Drs B and C, provided medical care to John Doe for recalcitrant psoriasis. At various times, Doe presented with localized psoriasis; other times, he was hospitalized for near total-body erythroderma.

Doe eventually experienced a complication from one of the biologic agents he took to control his chronic recalcitrant psoriasis. After recovering from near death, he sought legal counsel and was advised to sue all of his former dermatologists for the ordeal.

He hired a law firm and signed the appropriate releases, and his attorney asked for copies of all the records from Drs A, B, and C. The compilation of 12 years’ worth of records totaled 433 pages.

The Board of Medical Examiners in the doctors’ jurisdiction does not stipulate an exact amount for fees charged for medical records. The regulation simply states that fees must be reasonable. The dermatologists ask for $3 per page, submit a bill for $1299, and state that the records will be sent once the fee is paid.

The law firm responds with a letter stating that fees will be paid once the records are received. The dermatologists refuse to send the copies and receive a letter back that says the law firm will sue them if the records are not sent. Drs A, B, and C do not respond. Before long, they receive a summons from their local court.

The crux of the case is that the dermatologists are being sued for excessive fees for copies of their medical records. They are shocked. What can they do?

Almost 20 years ago, the Supreme Court of Mississippi ruled on a similar case. Owen & Galloway, LLC, a law firm, filed a lawsuit against defendants Smart Corporation, a medical records company; Gulf Coast Community Hospital, Inc; and Hancock Medical Center, alleging, among other issues, that excessive fees were being charged to the firm for copying and submission of medical records, in violation of Mississippi’s antitrust laws. The firm sought injunctive relief to immediately receive the medical records, attorney’s fees, $10 million in actual damages, and $15 million in punitive damages.

The initial trial court granted summary judgment to the defendants, in essence throwing out the case. The court noted that the firm lacked standing because as a matter of law, Owen & Galloway had no independent right to purchase copies of medical records was in its capacity as an agent for its clients. Thus, the court found that the real parties of interest were the clients, not the law firm. The firm itself did not have the right to object to the pricing structure of the medical records.

What the court did not answer was whether the clients would win such a lawsuit. Many state boards of medical examiners provide a fee structure for copying medical records, which should be followed strictly. Of note, many physicians copy records for patients at no charge, although they have no obligation to do so. However, in a state such as that of Drs A, B, and C, where the regulation requires only reasonable charges, there must be a correlation between the actual overhead costs and the charged fee.

The situation becomes more complicated with today’s electronic medical records (EMRs). Many boards of medical examiners ask for "written" records. In general, printed EMRs will be accepted. However, it is important that [these] records [were] electronically closed out at the time the patient was seen.
Microneedling Misconceptions

by ZOE DIANA DRAELOS, MD
Draelos is an adjunct assistant professor of dermatology at Duke University School of Medicine in Durham, North Carolina, and chief medical editor of Dermatology Times®.

Q: Should patients add microneedling to their regular moisturizing routine?
Microneedling is the use of sharp plastic or stainless-steel needles to porate the stratum corneum skin barrier, creating columns of controlled skin damage that encourages collagen regeneration and enhances penetration of ingredients. It can be performed with a handheld roller, a mechanized motor that pushes the needles back and forth, or a professional device that combines poration with other energy types, such as radiofrequency. Consumer and dermatologist-administered devices are available.

Microneedling has been touted to the consumer as a means to enhance the penetration of moisturizers, vitamins, skin-lightening ingredients, and other cosmeceuticals. Is this enhanced penetration good? It depends.

Microneedling has been touted to the consumer as a means to enhance the penetration of moisturizers, vitamins, skin-lightening ingredients, and other cosmeceuticals. Is this enhanced penetration good? It depends.

I do not think a normal moisturizer is suitable for microneedling. Most moisturizer formulations are designed to function as a thin layer over intact skin. Their role is to retard transepidermal water loss, which is not possible when the ingredients are microneedled into the skin. Special microneedling products that are devoid of preservatives—meaning they must be refrigerated or in individual-use pouches—and contain ingredients suitable for systemic absorption must be purchased. Many microneedling solutions use vitamins such as vitamin C for this purpose. Vitamin C is challenging to stabilize the oily ingredients into the dominant water phase are all weak surfactants.

Microneedling presents many consumer challenges, and both the device and the solutions should be carefully examined by a dermatologist for suitability and safety.

Q: Should patients microneedle with sunscreen on their face?
Patients definitely should not microneedle while wearing facial sunscreen. Sunscreens, which are designed to absorb and/or reflect solar radiation, work only on the skin surface and not in the skin; their ingredients are for topical application only and not intended for systemic absorption. Particulate inorganic sunscreens, such as titanium dioxide and zinc oxide, are not safe for entry into the skin—neither are organic sunscreens, such as oxybenzone, homosalate, and octyl methoxycinnamate. To prevent inadvertent penetration of unwanted chemicals and infection, patients should perform microneedling only on a freshly washed face.

Q: Should dermatologist-administered microneedling be performed before or after product application for maximal results?
Whether professionally administered microneedling should be done before product application or afterward remains controversial. One method involves painting the skin with a suitable microneedling solution and then microneedling over the solution, theoretically pushing the ingredients into the skin. The other option is to microneedle first to create holes in the skin and then paint the solution over the porated skin to enhance penetration. After microneedling, the pores created do not stay open for very long, because the skin is highly elastic and snaps back to close the pore very quickly. On the other hand, the needles do not cover every square inch of the skin surface, so the amount of prepped solution that penetrates the skin when the microneedling is performed is also limited. In conclusion, I would say that the penetration of ingredients via microneedling is somewhat limited.

Q: Should patients microneedle to their regular moisturizing routine?
Microneedling requires a preserved formulation with parabens kill bacteria and will also damage the viable skin. Do you really want surfactants in your skin? Emulsifiers that solubilize the oily ingredients into the dominant water phase are all weak surfactants.

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Qualified and Nonqualified Retirement Plans: Why Many Dermatologists Should Use Both... but Don’t

by DAVID B. MANDELL, JD, MBA; AND CAROLE C. FOOS, CPA

Mandell is an attorney and founder of the wealth management firm OJM Group in Cincinnati, Ohio, where Carole C. Foos, CPA, is a partner and tax consultant.

It is not surprising that data from national surveys show that the No. 1 financial objective for most US physicians is to achieve a financially secure retirement on their terms. OJM Group’s work with more than 1500 physicians across the country supports these findings.

What is surprising is the number of doctors, including dermatologists, who attempt to reach this goal using just 1 of the practice tools at their disposal: qualified retirement plans (QRPs). Many are completely unaware of another option: nonqualified plans (non-Q plans).

Understanding the structures of both types of plans is essential because the choice can have a significant impact on retirement.

QUALIFIED PLAN BASICS

The term qualified retirement means that the plan meets the definition of a retirement plan under Department of Labor and Internal Revenue Service rules created under the Employee Retirement and Income Security Act of 1974. A QRP may be in the form of a defined benefit plan, profit sharing plan, money purchase plan, 401(k), or (common in hospitals) 403(b). Properly structured QRPs offer a variety of benefits: Contributions to a traditional QRP are fully deductible, and the funds grow tax deferred and (if nonowner employees participate) enjoy superior asset protection.

On the other hand, disadvantages of these plans include the following:

- Mandated maximum annual contributions for defined contribution plans
- Mandatory employee participation
- Potential liability for management of employee funds
- Controlled group and affiliated service group restrictions
- Penalties for withdrawal prior to age 59½
- Required distributions beginning at age 72
- Full ordinary income taxation of distributions
- Full ordinary income taxation and estate taxation of balances upon death (combined tax rates can be more than 70%)

In OJM Group’s experience, most dermatologists participate in traditional QRPs despite these disadvantages. The tax deduction is a strong, often irresistible lure. For many, however, the cost of contributions for employees, potential liability for mismanagement of employee funds, and ultimate tax costs on distributions may outweigh the current tax savings offered by QRPs. If not giving pause, these drawbacks at least suggest that it would make sense to investigate another type of plan (to hedge the QRP) as an additional savings vehicle.

With a traditional QRP [qualified retirement plan], a participant trades today’s tax rates on their contribution for the tax rates in the future, when they withdraw the money from the plan. If rates rise, the QRP might prove not to be a good deal at all.

Although no one knows what the future will bring, it is a fact that tax rates were much higher for most of the second half of the 20th century than they are today. Conversely, the federal deficits are higher today than ever before because of the stimulus packages related to the COVID-19 pandemic. At some point, taxes will need to be collected to pay down these deficits.

Furthermore, most dermatologists will not see a drastic change in marginal tax rates during retirement (Figure). In fact, it appears that most physicians work and save until they have a “comfortable” retirement. Although every physician defines their retirement goal differently, it is rare that specialists such as dermatologists retire with income that puts them in a lower tax bracket.

In fact, their retirement income from passive investments, sale of assets, Social Security, and QRP distributions often puts them in one of the top marginal tax rates. For these reasons, many dermatologists should use retirement savings alternatives to hedge against retirement income from their QRPs.
ROTHS
One alternative is a Roth IRA or Roth component to a QRP. Taxes are paid up front on any contributions, but the Roth balance grows tax free and can be accessed tax free in retirement. Compared with the tax treatment of QRPs, the Roth's tax-free access can be tremendously valuable. Existing rules limit how much money can go into this type of vehicle. Further, tax bill provisions may curtail or eliminate many taxpayers' ability to use a Roth. It is important to work with an experienced tax adviser when considering this option.

NONQUALIFIED PLAN BASICS
Non-Q plans are not used by physicians nearly as much as by corporate executives. This is unfortunate, because they could be valuable retirement tools for many dermatologists. These plans are not subject to QRP rules, so they do not have to be offered to employees. Even for physician-owners, there is total flexibility. For example, one practice owner can contribute the maximum, the next partner could put in much less, and a third physician could opt out. These are the reasons large corporations use non-Q plans so often: They can choose which executives get to participate and at what levels.

The main drawback of non-Q plans is that contributions are generally not tax deductible. However, as with a Roth IRA, they can be structured for tax-free growth and tax-free access in retirement. For someone who would fund a Roth beyond current limitations, a non-Q plan could be an attractive option.

Consider the following attributes of a non-Q plan:
- Places very few limitations on contributions as opposed to QRPs
- Can be implemented in addition to a QRP, such as a 401(k) or profit-sharing plan
- Lets owners/partners vary how much/if they participate
- Does not require employee participation
- Generally produces no tax deduction on contributions, but funds can both grow and be accessed tax free

ROTHS
Provides top asset protection in many states
Given all these attractive benefits, why do so few dermatologists use non-Q plans? In OJM Group’s experience, it is because advisers often do not bring them up to physicians as a planning option. Many certified public accountants are not well versed in non-Q plans, which create no immediate tax deduction so may not be on their radar. Further, the adviser who administers the practice’s QRP (the third-party administrator) is not typically needed in a non-Q plan, so it is rarely presented as an option.

Despite an adviser’s knowledge of non-Q plans, the underlying reason that these valuable retirement-planning tools often are not considered for medical practices is that few physicians think enough about long-term tax treatment and instead focus only on their tax liability for the current year.

CONCLUSION
Both QRP and non-Q plans can play important roles in building a secure retirement. An experienced adviser can lay out each type’s upsides and downsides and help determine which plan will best fit a practice’s needs and goals.

Disclosure
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FIGURE
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Rediscovering the Genetics of Acne

ILYA PETROU, MD | Staff Correspondent

The etiology of acne is complex and multifactorial, with genetics playing a large role in determining risk, particularly for individuals with severe acne. The results of a recent study further elucidated the genetics of acne and advanced the knowledge of related risk by identifying variants of genes that are common among individuals with this inflammatory skin disorder.

It is estimated that acne affects more than 85% of teenagers to some degree, with severe disease reported in up to 8%, making acne the most prevalent skin disease worldwide. Depending on its severity, acne can significantly affect self-image and quality of life. Major complications include scarring and, at times, significant psychosocial distress that can persist long after active lesions have disappeared from the skin.

“Approximately 80% of a person’s risk of [experiencing] severe acne can be explained by differences in their genetic makeup,” said Miguel E. Rentería, PhD, senior research fellow in the Department of Genetics and Computational Biology at QIMR Berghofer Medical Research Institute in Brisbane, Australia, and coauthor of the study. “It is not a single gene but, rather, variations across hundreds of genes in the genome that determine whether someone is likely to get acne and the extent or severity of the condition.”

Rentería and colleagues recently performed a large meta-analysis of genome-wide association studies of acne undertaken in 9 independent cohorts. The 615,396 participants consisted of 20,165 patients with acne and 595,231 controls, making it the largest study of its kind, with the aim of identifying genetic associations with severe acne. The results of a recent study further elucidated the genetics of acne and advanced the knowledge of related risk by identifying variants of genes that are common among individuals with this inflammatory skin disorder.

Identifying additional genetic variants for acne could lead to new targets for treatment and pinpoint patients at higher risk of severe disease. Personalized acne treatments based on genetic profiles are still a few years off.

Fifteen of these loci have been reported to have an effect in European populations. This highlights potential differences in the genetic architecture of acne between different ethnic populations, warranting further investigation in studies of diverse ancestry. According to Rentería, however, one of the main limitations is the lack of availability of cohorts or biobanks focused on diverse ancestries.

“Our study results highlight possible molecular pathways that are implicated in acne, opening new avenues for fundamental research and development of therapeutic targets,” Rentería said. “Looking forward, we could apply this knowledge to do genetic tests of acne risk and identify those individuals who are likely to present with acne.”

Novel research studies must be designed and performed to better clarify the role of the newly identified acne genes, including characterizing the variants’ mechanisms of action and assessing their potential as therapeutic targets to treat acne, he said.

According to Rentería, the estimation of individual genetic acne risk scores relative to the general population might be the most immediate application of the current study findings. “We demonstrated that it is possible to use a person’s genetic information to estimate their genetic risk of developing acne based purely on which genetic variants they inherited from their parents,” Rentería said. “In the future, we will be able to identify those individuals who are at high risk of acne many years before they even notice the first signs.”

Finding genes implicated in acne is the first step toward patient stratification and personalized medicine. Although research has been inching closer toward targeted medicine on the genetic level, fulfillment is likely a few years away. A clinician’s treatment and management choices in the future could be informed by a patient’s genetic profile, Rentería said, adding that much work remains regarding characterizing the genetic basis of different acne types and treatment response across life stages.

“This research enables a much better understanding of the genetic basis of acne, and investigation of these variants further illustrates the shared biology processes with other skin and hair traits, as well as a shared genetic etiology with other common diseases,” Rentería said. “However, identifying the relevant genes is not the end but, rather, the beginning of a journey of discovery.”

Reference
Perspectives on the Rosacea Pipeline

LINDA STOCUM | Associate Editor

Rosacea might be a common condition, but its complex pathophysiology makes it difficult to design a standard treatment, according to Richard Gallo, MD, PhD, chair of the Department of Dermatology at the University of California, San Diego, and a member of Dermatology Times editorial advisory board. Both patient genetics and the trigger composition contribute to the uniqueness of this multifactorial skin disease, Gallo explained in an exclusive interview with Dermatology Times. This individuality of disease is defined by different rosacea diagnostic or major phenotypes, which include the following:

- Persistent redness in the central area of the face, which can recur and can appear as purple or brown in darker skin types
- Skin thickening, including phymatous changes such as distended follicles (enlarged pores), fibrosis, glandular hyperplasia (enlarged facial oil glands), and a bulbous nose
- Papules and pustules that often appear on the cheeks, nose, forehead, and chin
- Visible telangiectasia
- Frequent or prolonged flushing
- Eye symptoms representing a spectrum of disease, such as meibomian gland dysfunction; visible blood vessels on or around the eyelid margin; bloodshot eyes; hazy, spade-shaped areas in the normally clear cornea; and redness and inflammation of the whites

PROGRESS REPORT
“We’ve made a lot of progress over the past several years... but the erythema [and] flushing remain difficult to treat,” Gallo said. The COVID-19 pandemic slowed movement in the pipeline: The last approval for rosacea was in May 2020 for FMX103 (Zixi; Menlo Therapeutics), a 1.5% minocycline foam, for the treatment of inflammatory lesions of rosacea in adult patients. The Prescription Drug User Fee Act date for Epsolay, a 5% encapsulated benzoyl peroxide foam, was due in 2021, but on April 26, 2021, the action was officially delayed because of FDA restrictions. A tour of the company’s manufacturing facilities was scheduled for February 14, 2022, but there has been no further news on the FDA decision.

Advances in drug delivery, such as how particles are sized and components are packaged, have led to improved tolerability and effectiveness, according to Gallo. For example, he said, before microencapsulation, benzoyl peroxide was too harsh for patients with rosacea, but when delivered in a consistent, controlled way that increases tolerability, it can target microbial colonization, a trigger of the disease. Benzoyl peroxide, based on current data, is improving the treatment of the papular and pustular phenotype of rosacea but flushing remains difficult to treat, Gallo said.

“Using the antimicrobial approach topically limits systemic effects on the microbe that might be deleterious and can occur with oral antibiotics,” Gallo said. “It also avoids the effects that immunomodulators may have on the disease.” However, overall, benzoyl peroxide is expected to be a safe, well-tolerated option.

RISK ASSESSMENT
Possible signs of adverse events include exacerbation of disease or evidence of irritation from the chemical itself, he explained. Because rosacea is so sensitive, factors such as sunlight, heat, ingestion of spicy foods, and colonization by the wrong kind of microbes can trigger the inflammatory response. When onboarding a patient, it is essential to get a full picture of current lifestyle choices and discuss modifications to potentially eliminate disease triggers, Gallo said.

It is also important to factor in the patient’s potential sensitivity when deciding on the right treatment, he added. If a patient is very sensitive, Gallo might consider a slow start; if the skin seems more tolerant, he might prescribe a full-dose regimen and then taper down.

Gallo expects to see more studies of the individual genes that trigger rosacea, especially because of the variability in the phenotype of disease, he said: “[As with] so many aspects of medicine, we’re moving toward trying to get to a personalized approach. It would be wonderful to be able to implement that in rosacea.”

Gallo noted that there are many reapplications of past medications as well as different targets in the pathophysiology. There may be new ways to control the microbial colonization that do not require standard antibiotics; perhaps different kinds of probiotics or prebiotics, hormonal modulation, and protease inhibitors could be added to the armamentarium for rosacea therapy, he said.

References
Is Rosacea Hereditary?

Investigators report that the effect of family history is more significant than thought.

LINDA STOCUM | Associate Editor

Familial prevalence may play a larger role in an individual’s predisposition to develop rosacea than previously thought, according to recent findings published in the *Journal of Clinical and Aesthetic Dermatology*. The investigators in the retrospective observational study assessed familiarity and interfamilial transmission up to 6 generations—a first for this type of research, according to the study investigators.

The study included patients affected by rosacea from June 2018 to June 2019 and focused on demographic data regarding characteristics, anamnestic findings, and clinical results, including severity grade, according to global Rosacea Consensus recommendations. In most cases, all affected relatives, including children, were examined clinically. Those not available for in-person consultations submitted photos.

Based on the results, the investigators considered the following modalities:

1. **Horizontal transmission**, encompassing all family members not directly descended from the proband, defined as a patient for whom at least 1 family member has rosacea.

2. **Vertical transmission**, including all family members directly descended from the proband in an ascending and/or descending trend.

3. **Combination of vertical and horizontal transmission of disease**.

Overall, 130 patients (37 male, 93 female; mean age, 49.3 ± 18.6 years; range, 18-85 years) were enrolled into the study. Fixed centrofacial erythema and telangiectasias with papules/pustules lesions were the predominant phenotype in 67 patients (51.5%), followed by fixed centrofacial erythema and telangiectasias in 49 (37.8%), phymatous changes in 5 (6.9%), and ocular manifestations in 9 (3.8%), the investigators wrote.

Severity of rosacea was mild in 45 cases, moderate in 70, and severe in 15. A statistically significant association was found between fixed centrofacial erythema and telangiectasias with papules and pustules phenotype and female gender (P = .0001).

Additionally, statistically significant associations were observed with phymatous changes with male sex (P = .0001), normal weight (P = .009), and smoking (P = .026), as well as ocular symptoms with alcohol consumption (P = .01).

Of the 130 patients, 64 (49.2%) probands were positive for at least 1 family member. Of this group of 64 probands, 28 (43.8%) had issues with fixed centrofacial erythema and telangiectasias, 26 (40.6%) with fixed centrofacial erythema and telangiectasias with papules/pustules and 1 each (1.6%) with ocular manifestations and phymatous changes in patients, respectively.

Severity scores were mild in 21 (32.8%) cases, moderate in 35 (54.7%), and severe in 8 (12.5%). A statistically significant association was found between familial rosacea and fixed centrofacial erythema and telangiectasias, papules/pustules lesions (P = .005), and alcohol consumption (P = .01), the investigators wrote.

An accurate familial anamnestic investigation of the whole kindred in the probands group identified 90 relatives (69.2%) as affected. Of that total, 45 (50%) showed fixed centrofacial erythema and telangiectasias; 32 (35.5%), fixed centrofacial erythema and telangiectasias with papules/pustules; and 10 (11%) and 3 (3.5%), ocular manifestations and phymatous changes, respectively. The severity rate was mild in 39 patients (43.6%), moderate in 42 (46.6%), and severe in 9 (10%). Data revealed a statistically significant association between phymatous changes and male gender (P = .0001).

For rosacea inheritance, vertical transmission was found in 45 (70.3%) probands, horizontal transmission in 11 (17.2%), and combined transmission in 8 (12.5%). When looking at ascending, descending, and combined ascending/descending vertical transmission, 36 patients were identified—45 of the relatives were ascending; 7, descending; and 4, a combination. Overall, in the vertical transmission group, maternal lineage was predominant compared with paternal (29/45.3% vs 21/32.9%). In the horizontal transmission group of 13 relatives, 2 pairs of fraternal twins were observed, and 21 relatives were involved in combined horizontal/vertical transmission, the investigators wrote.

“Based on our data, the prevalence of familial rosacea was 69.2%, with a ratio of affected relatives equal to 1:1.4,” the investigators concluded. “We believe that the prevalence of rosacea familiarity is underestimated and that a more accurate investigation among multiple family generations is advisable.”

**Reference**


**Prevalence of Rosacea Patients in the Probands Group**

<table>
<thead>
<tr>
<th>Severity Category</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>21</td>
<td>32.8%</td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>54.7%</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

**Prevalence Rate**

69.2%
Head-to-head superiority for full body relief

Recommend a superior formulation that significantly outperforms in immediate and lasting hydration

Ask your sales representative to see the head-to-head data

Superior hydration | For daily moisturization | NMFs + Ceramide NP

NMFs=natural moisturizing factors.
Groundbreaking AAD Guidelines Assess Links Between AD, Comorbidities

Part 2 of our coverage on the American Academy of Dermatology’s new guidance focuses on the association between atopic dermatitis and comorbidities such as mental health issues, metabolic disorders, and bone health.

LINDA STOCUM | Associate Editor

In recently released guidelines, the American Academy of Dermatology (AAD) aims to raise awareness of the comorbidities of atopic dermatitis (AD). The March issue of Dermatology Times® reported on the new guidance on AD and its association with atopic and allergic conditions, immune-mediated conditions, and cardiovascular diseases. The academy’s multidisciplinary work group evaluated the evidence supporting these comorbidities as the first of a 4-part series and discovered possible stronger evidence to support some of the investigated associations.

The work group used the Grading of Recommendations, Assessment, Development, and Evaluation to determine the certainty of evidence and then, based on the certainty and strength of the data, delivered statements on the associations.

This second part of Dermatology Times® coverage highlights possible connections between AD and issues ranging from mental well-being to bone health.

MENTAL HEALTH
Various studies have investigated the likelihood of patients with AD to experience depression and anxiety. After analyzing 4 studies that included 11,244 adults with AD and 149,713 controls, the work group found that AD was associated with double the odds of self-reported or clinician-diagnosed depression (odds ratio [OR], 1.99; 95% CI, 1.53-2.59).1 Pooling 4 studies with 157,222 adults with AD and 300,719,113 controls showed similar data for anxiety (OR, 1.40; 95% CI, 1.12-1.75).1

The work group found that adult patients with AD were more likely to have suicidal thoughts than adults without AD (OR, 1.71; 95% CI, 1.43-2.03). However, there is less evidence on an association with death from suicide, and study results were conflicting.2-5 Although the reasons for the association between AD, depression, and anxiety remain undetermined, a possible explanation is the psychological burden of itch, poor sleep, and decreased quality of life caused by the skin condition. This is supported by data from clinical trials that found that an improvement in AD reduced symptoms of depression and anxiety in patients with moderate to severe AD.6,7

Takeaways on AD and mental health
In adults, AD:
- is associated with clinician-diagnosed depression (moderate-quality evidence).
- is associated with clinician-diagnosed anxiety (moderate-quality evidence), and
- may be associated with suicide (low-quality evidence).

SUBSTANCE USE
The work group considered both national and international research on AD and substance use. Findings of a Danish population study showed that alcohol abuse was more common in adult patients with AD (OR, 1.38; 95% CI, 1.24-1.53), whereas results of a US population-based survey found that the alcohol intake
of adults with AD was more likely to be moderate (OR, 1.33; 95% CI, 1.09-1.62) and heavier (OR, 1.58; 95% CI, 1.23-2.03) compared with controls.9

Regarding smoking, results of a US-based population survey revealed that AD was associated with smoking more than 100 cigarettes (OR, 1.32; 95% CI, 1.18-1.47) in one’s lifetime and being a current smoker (OR, 1.28; 95% CI, 1.12-1.45).

The work group commented that most studies on the link between alcohol use and smoking are cross-sectional, making causality difficult to determine. “As with depression and anxiety, an association [with alcohol and cigarette smoking] could be explained by the burden of AD increasing patients’ likelihood of engaging in those harmful behaviors,” the work group stated. Results of a cohort study on US nurses found no association between cigarette smoking and developing AD.10

**Takeaways on AD and substance use**

**ADHD AND AUTISM**

Currently, more research is available on associations between AD and attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders in the pediatric vs adult patient population. The associations for pediatric patients with AD and these comorbidities will be covered in a future practice guideline according to the AAD.

Just 2 studies were available on possible links, and only 1—a US population-based trial—examined the association of ADHD in adults and included controls from the general population.11,12 Those results did reveal an association (OR, 1.61; 95% CI, 1.25-2.06) compared with controls.11

**Takeaways on ADHD and autism**

In adults, AD:

- may be associated with ADHD (low-quality evidence) and
- has an uncertain association autism spectrum disorders (very low-certainty evidence).

**METABOLIC DISORDERS**

Current evidence suggests a small link between adult AD and obesity and dyslipidemia. Data from 8 cross-sectional studies pooled by the work group found an association with 30% increased odds of obesity (OR, 1.36; 95% CI, 1.01-1.83) and 13% increased odds of hypercholesterolemia (OR, 1.13; 95% CI, 1.09-1.18) compared with the general population.1 It currently is unclear whether AD severity affects the association of obesity.1,3,14 The link may vary geographically because of factors that vary by location.15

Just 2 studies compared metabolic syndrome in people with and without AD.16,17 AD may have an inverse association with diabetes. The work group found AD to be associated with a lower risk of diabetes overall (OR, 0.89; 95% CI, 0.80-0.99) and type 2 diabetes specifically (OR, 0.83; 95% CI, 0.76-0.90).1

**Takeaways on AD and metabolic disorders**

In adults, AD:

- is probably associated with obesity (moderate-quality evidence),
- is probably associated with dyslipidemia (moderate-quality evidence),
- may not be associated with diabetes (low-quality evidence), and
- has an uncertain association with metabolic syndrome (very low-quality evidence).

**SKIN INFECTION**

The link between AD and staphylococcal skin infection is well established.18 Herpes skin infection (HSV or eczema herpeticum) is a more severe complication of AD.19 Findings of a UK cohort study revealed HSV infections to be more than twice as common among people with AD compared with general population controls, the work group said.12

According to data from hospitals across the United States, AD is also associated with serious cutaneous infections—defined as leading to hospitalization or as life-threatening—that require treatment in an inpatient setting (OR, 4.62; 95% CI, 4.51-4.74).1 It was also found that bacterial skin infections and HSV are more likely to occur with poorly controlled dermatitis; if treatment is successful it may lower the incidence rates of these infections.21

**Takeaways on AD and skin infection**

In adults, AD is associated with skin infection (moderate-quality evidence).

**BONE HEALTH**

Taiwanese investigators reported an increased risk of patients with AD developing osteoporosis (HR, 4.72; 95% CI, 3.68-6.05) compared with the general population.22 Also, results of a UK cohort study found that the risk of fracture associated with AD was modestly increased overall (HR, 1.07; 99% CI, 1.05-1.09) and slightly higher among those with severe AD (HR, 1.22; 99% CI, 1.14-1.30).23 The risk was much higher for osteoporosis-related fractures, with severe AD associated with 200%, 66%, and 50% increased rates of spinal, pelvic, and hip fractures, respectively.24

Although investigators have examined numerous potential factors regarding a link between AD, osteoporosis, and fractures, further research is needed to determine the true mechanism of association.

**Takeaways on AD and bone health**

In adults, AD:

- is associated with osteoporosis (high-quality evidence) and
- is associated with bone fractures (moderate-quality evidence).

"As with depression and anxiety, an association [with alcohol and cigarette smoking] could be explained by the burden of AD increasing patients’ likelihood of engaging in those harmful behaviors."
THE ONE-OF-A-KIND TOPICAL JAK INHIBITOR

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

> Clear or almost clear skin (IGA 0/1)* in >50% of patients at week 8 (53.8% vs 15.1% and 51.3% vs 7.6% vehicle†; P<0.0001)1,2

> Meaningful itch relief (Itch NRS4) in >50% of patients at week 8 (52.2% vs 15.4% and 50.7% vs 16.3% vehicle†; P<0.0001)1,2

– Itch NRS4 response seen as early as day 3 (18.4% OPZELURA vs 4.2% vehicle and 13.2% OPZELURA vs 0% vehicle†)3

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

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

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

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INDICATION

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

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

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

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

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

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

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

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

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

Please see additional Important Safety Information on following page.

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on following pages.
SERIOUS INFECTIONS (continued)

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

MORTALITY

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

MALIGNANCIES

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

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

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

THROMBOSIS

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

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

Thrombocytopenia, Anemia and Neutropenia

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

Lipid Elevations

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

Adverse Reactions

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

Pregnancy

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

Lactation

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

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

**Opzelura™ (ruxolitinib) cream 1.5%**

**OPZELURA™ (ruxolitinib) cream, for topical use**

**Brief Summary of FULL PRESCRIBING INFORMATION**

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

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

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

**SERIOUS INFECTIONS**

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

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

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

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

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

**MORTALITY**

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

**MALIGNANCIES**

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

**MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)**

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

**THROMBOSIS**

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

**WARNINGS AND PRECAUTIONS**

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

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

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

**Hepatitis B and C:** The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials. Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

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

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

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

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

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

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

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

**ADVERSE REACTIONS**

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White. 23% were Black, and 4% were Asian. The serious reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499): vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bradycardia 4 (1%) vs 0 (0%), Tachycardia 6 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Cough 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Fatigue 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

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

**DRUG INTERACTIONS**

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

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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

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

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

**Data**

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

**Lactation**

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

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

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

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

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

**PATIENT COUNSELING INFORMATION**

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

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

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

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

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

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

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

Advise patients to limit treatment to 60 grams per week.

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

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

The investigators wrote that although a lack of evidence for predictive biomarkers of the studied treatments “should not be interpreted as evidence of an absence, our results suggest that the effect of biomarkers on the prediction of severity scores, if any, is likely be small or too subtle to be captured by our linear model, [given that] the prediction errors of future scores by our model were mostly attributed to errors in the score measurement process.” Data from a larger cohort could better inform future research into the effect of biomarkers on severity score prediction in AD, they added.

Study limitations included the small patient population; however, the investigators noted that the AD severity scores were assessed at 6 time points, suggesting a methodological strength.

Nakamura said that although biomarkers may identify whether certain treatments will be successful for specific patients, this information must be balanced with each patient’s treatment goals and preferences. “For example, even if science shows that the patient would do best on dupilumab [Dupixent; Sanofi and Regeneron Pharmaceuticals], if the patient is needle-phobic, dupilumab wouldn’t be an option, and the same would be true if the patient has comorbidities that are contraindications to certain therapies,” she said. “Even if we can develop scientific ways to stratify AD patients and predict treatment outcomes, we will still need to see how to best utilize these means in the real-life setting.”

“What we are increasingly finding for AD specifically is that it’s a heterogeneous disease, and there are a lot of different factors that can affect the specific and individual immune profile,” Nakamura continued. “Because of that, what we’re seeing is that there’s no one-size-fits-all approach to treatment for the condition.”

Benjamin Ungar, MD, assistant professor of dermatology and director of the Rosacea & Seborrheic Dermatitis Clinic at Mount Sinai in New York, New York, explained in an interview with Dermatology Times® that certain predictive biomarkers could help direct selection of treatment and therefore be an important aspect of personalized care in AD.

Although the new study did not find the examined biomarkers predictive of treatment response in AD, Ungar, who was not involved in the study, stated that the findings do not close the door on use of biomarkers in this disease. “One thing that we are seeing with the research—and this is work that we have done at Mount Sinai—is that biomarker associations with disease severity and treatment response are really the best when they combine both blood [and] skin biomarkers,” Ungar explained. “I think moving forward, continued efforts to identify these biomarkers from multiple different areas and multiple different approaches are going to be needed to improve that kind of capability.”

Disclosures
Nakamura and colleagues report no relevant conflicts of interest. Nakamura and Ungar report no relevant conflicts. The study was funded by the British Skin Foundation.

Reference
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Annenberg Circle continued
Psoriasis and Cardiometabolic Disease Share Inflammatory Basis

From its pathophysiology to its relationships with cardiovascular risk factors, psoriasis may offer a clear view of vascular health.

Bob Kronemyer | Staff Correspondent

Results of recent research showcase the importance of psoriasis “as a model for the cardiovascular consequences of chronic inflammation,” according to the study authors.1

“Inflammation plays a critical role, from initiation to progression to rupture of atherosclerotic plaques,” wrote the authors from the National Heart, Lung, and Blood Institute of the National Institutes of Health in Bethesda, Maryland. “The progression and stability of these plaques depends on the balance between pro- and anti-inflammatory forces.”

Inflammation is also linked to risk factors for atherosclerosis; for example, hyperlipidemia, hypertension, and obesity promote inflammation and are more prominent with chronic inflammation.

Likewise, psoriasis leads to systemic and vascular inflammation as well as a higher risk of cardiometabolic diseases than in the general population, with the greatest difference in risk among younger patients with severe psoriasis.2

Patients with psoriasis have a complex interplay with metabolic syndrome, a group of risk factors that is strongly connected to future risk of cardiovascular events. Both psoriasis and metabolic syndrome have a higher coronary subclinical atherosclerosis burden that increases in a stepwise manner with each additional criterion met.1

The relationship between psoriasis and obesity is complicated: Some findings indicate obesity is a risk factor for psoriasis, whereas others suggest that obesity is a cause of the disease. Regardless, psoriasis and obesity share common inflammatory pathways.

The psychosocial impact of living with psoriasis, including depression, anxiety, and stress, can contribute to body fat distributions that have an unfavorable cardiometabolic profile. Joint involvement also may curtail regular physical activity.

The metabolic syndrome component related to central adiposity may be the initiating factor for cardiometabolic disease. Abdominal visceral adipose tissue, for instance, has been associated with systemic inflammation in psoriasis and may play a crucial role in insulin resistance, hyperlipidemia, and hypertension. A strong association also exists between metabolic syndrome and abdominal visceral adipose tissue volume in psoriasis.3

Because inflammation alters lipid structure and function, it can lead to increased production and decreased clearance of triglycerides. It also can change the content and function of high-density lipoprotein cholesterol (HDL).

Patients with psoriasis have higher triglycerides and lower serum HDL levels compared with the general population. HDL cholesterol efflux capacity is impaired in psoriasis and negatively correlates with the Psoriasis Area and Severity Index (PASI) score.4

Similarly, because chronic inflammation hinders insulin signaling and promotes insulin resistance, patients with psoriasis have a higher prevalence of type 2 diabetes and elevated blood glucose and insulin compared with controls, according to the investigators.

Inflammation also plays a major role in hypertension, with the 2 conditions sharing important inflammatory pathways. In addition, although some study results have shown...
Inflammation plays a critical role, from initiation to progression to rupture of atherosclerotic plaques.

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a higher prevalence and risk of hypertension in patients with psoriasis, some evidence suggests that hypertension also may be a risk factor for psoriasis, the authors wrote.

Anti-inflammatory psoriasis therapy can reduce vascular inflammation and high-risk coronary atherosclerosis burden, as well as some components of metabolic syndrome. After 6 months of anti–tumor necrosis factor α (anti–TNF-α) therapy, patients with psoriasis have shown an improvement in insulin sensitivity. The authors noted that, in a separate cohort of patients with psoriasis or rheumatoid arthritis, anti–TNF-α therapy achieved a lower incidence of diabetes.

Although there is some evidence that biologic therapy might reduce systolic and diastolic blood pressure in patients with inflammatory conditions, anti–TNF-α therapy could be linked to a higher risk of hypertension in rheumatoid arthritis, according to the authors.

Meanwhile, anti-inflammatory psoriasis therapy may reduce rates of cardiovascular events. However, certain biologic therapies might have lower efficacy in patients with psoriasis and a higher body weight or body mass index.

Because of the significance of the adiposity component of metabolic syndrome, investigators recently evaluated the efficacy and safety of biologic therapies based on metabolic syndrome status. For instance, results of 2 phase 3 randomized controlled trials of tildrakizumab (Ilumya; Sun Pharma) showed that the percentage of patients with chronic plaque psoriasis who had at least a 75% improvement in PASI score at 12 and 52 weeks was comparable with metabolic syndrome status. The reduction in psoriasis severity from baseline was also similar in those with and without metabolic syndrome.

Based on these factors, the authors emphasized “the need for heightened awareness of these consequences amongst patients and providers and the value of further study of this disease state to understand the role of inflammation and anti-inflammatory treatment on cardiometabolic health.”

References

Effect of Joint Pain on Analgesic Use in Patients With Psoriasis

BOB KRONEMYER | Staff Correspondent

Joint pain appears to be the reason patients with psoriasis, especially those with concomitant psoriatic arthritis (PsA), take analgesics more frequently than the general population, according to findings of a cross-sectional study published in the *Journal of the American Academy of Dermatology*.

“We knew from previous studies that patients with psoriasis have a higher use of analgesics than the general population, but the reason had not been well described,” said principal investigator Nikolai Loft, MD, PhD, senior researcher in the Department of Dermatology and Allergy at Copenhagen University Hospital–Herlev and Gentofte Hospital, both in Denmark.

“Joint pain is common among patients with psoriasis, both those with psoriatic arthritis and those without,” Loft told *Dermatology Times*. “This joint pain is associated with use of analgesics and impaired general health, whereas skin symptoms are associated with worse quality of life (QOL) to a higher degree than the affected body surface.”

To gain further knowledge on this subject, investigators aimed to assess the symptoms, disease burden, and use of analgesics in patients with and without PsA. The study population from the Danish Skin Cohort included 4,016 patients with psoriasis, of whom 21.1% (n = 847) also had PsA, and a control group of 3,490 individuals without psoriasis.

The mean age of the general population was 54.7 years vs 59.4 years in the psoriasis population. Additionally, 55% of the comparison group were women vs 56% of psoriasis group.

At the time of self-assessment, 47% of patients with psoriasis reported mild disease; 25.4%, moderate; and 27.6%, severe.

Symptoms, general health, and analgesics use were assessed in all participants. General health was measured via EuroQol 5-Dimension 5-Levels (EQ-5D-5L), encompassing 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Psoriasis located on the face, hands, genitals, and feet was linked to itch and skin pain. Patients with psoriasis, PsA, itch, skin pain, and/or joint pain had worse general health, according to the findings.

The percentages of the general population reporting moderate to severe skin pain, itch, and joint pain were 7%, 10%, and 35% respectively. In contrast, among patients with psoriasis, moderate to severe skin pain was reported by 30% with PsA and 21% without PsA, respectively ($P < .0001$); moderate to severe joint pain by 69% and 45%, respectively ($P < .0001$), and moderate to severe itch by 34% and 30% ($P = .022$), respectively.

Based on EQ-5D-5L results, general health was worse in patients with psoriasis compared with the general population across all psoriasis severities (0.86 vs 0.90; $P < .001$) and significantly worse in patients with psoriasis and PsA than those without PsA (0.80 vs 0.87; $P < .001$).

Joint pain had the highest impact on worsening general health. Symptoms originating from the skin and joints were associated with increased risk of reporting any problems in all EQ-5D-5L domains, with joint pain showing the strongest link to most domains.

As for disease burden, 47.6% of patients with psoriasis reported no effect at the time of assessment with the Dermatology Life Quality Index (DLQI); 30.3% reported a small effect; 12.7%, a moderate effect; 8.3%, a very large effect; and 1.2%, an extremely large effect.

There was no difference in DLQI among patients with PsA and those without PsA across psoriasis severity. However, patients with a higher percentage of affected body surface area (BSA) typically reported a higher impact on DLQI, with a weak to moderate correlation between BSA and DLQI.

In addition, skin pain and itch showed moderate correlations with DLQI, whereas joint pain had a negligible correlation.

Patients with more severe skin symptoms also reported a significantly higher impact on QOL, independent of psoriasis severity.

The number of prescriptions for the analgesic medication paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs, opioids, and gabapentin/pregabalin dispensed for participants was obtained for participants through an individual-level linkage with the nationwide Register of Medicinal Products Statistics, the investigators reported.

Patients with psoriasis used more analgesics than the general population, and patients with PsA used the drugs more than those without PsA. However, there was no connection between the extent of psoriasis and use of any of the examined analgesics. Prescription of several agents was associated with increasing severity of symptoms in both the skin and joints.

Opioid use within 12 months occurred in 9% of the general population, 14.2% of patients with psoriasis but not PsA, and 22.7% of patients with concomitant PsA.

For patients without PsA, 12.7% with mild or no itch had used opioids in the past 12 months at the time of the study; 12.9%, for skin pain ($P = .001$). For those with severe itch and pain, the corresponding percentages were 19.4% and 19.3% ($P < .001$).

The study results stated that only joint pain was associated with use of analgesics (odds ratio, 3.72; 95% CI, 2.69-5.14; $P = .0001$).

“We anticipated that patients with psoriasis would use analgesics more frequently for symptoms of both the joint and the skin, rather than simply for joint pain,” Loft said. “Treating physicians should be aware of symptoms, including those from the joint and the skin.”

Disclosure

Loft has been a consultancy speaker for Eli Lilly and Company and Janssen-Cilag.

For reference see dermatologytimes.com.
There’s a void for patients living with plaque psoriasis

Patients won’t benefit from treatments they don’t use

Learn more and share your perspective at RethinkTopicals.com
2022: Meeting the Challenges of Advanced BCC

MARY SCOVIAK  |  Managing Editor

Surgical options, especially Mohs surgery, and Hedgehog inhibitors have dominated the treatment landscape for advanced basal cell carcinoma (BCC). But not every patient is a good candidate for surgery, and, for others, tolerability and progression issues connected with Hedgehog inhibitors often pose challenges to long-term disease management. Now, with an increasing emphasis on multidisciplinary tumor review boards and heightened expectations for pipeline drugs, physicians have new tools for building treatment plans that may push response rates beyond the 30% range.

Three experts discussed these strategies in exclusive interviews with *Dermatology Times*®:

- Darrell S. Rigel, MD, MS, FAAD, a clinical professor and director of the Melanoma Surveillance Clinic at the Icahn School of Medicine at Mount Sinai in New York, New York
- Chrysalyne Schmults, MD, FAAD, a physician at Brigham and Women’s Hospital and an associate professor of dermatology at Harvard Medical School, both in Boston, Massachusetts
- Ann W. Silk, MD, MS, codirector of the Merkel Cell Carcinoma Center of Excellence at Dana-Farber Cancer Institute in Boston, and physician and an assistant professor of medicine at Harvard Medical School

**DIAGNOSIS AND MULTIDISCIPLINARY TEAM MANAGEMENT**

The vast majority of the more than 1 million BCC cases each year in the United States are “easily cured” with surgical excision, with “only about” a 1% recurrence risk, Schmults and Rigel noted. In their experience, of the 1% of BCCs that do recur, most resolve with a second excision.

However, for cases that fail after multiple surgeries, Rigel, Silk, and Schmults all favored the formation of a cross-disciplinary team to create a holistic care plan. “What we call ‘advanced’ BCC can mean that it is beyond the skill set of a Mohs surgeon alone,” Rigel told *Dermatology Times*®. “You may reach a point where you are getting positive margins everywhere or where the lesion is large enough to require an inpatient procedure to try to repair it.”

If that is the case, Rigel suggested setting up a multidisciplinary management team that includes the dermatologist who made the advanced BCC diagnosis, a Mohs surgeon, a surgical oncologist, and a radiation oncologist.

Schmults agreed, noting a recent case from a tumor board at which a patient presented with a high risk of recurrence.

“In the future, studies are investigating potentially debulking these large lesions. At some point, there will be some combination of factors that work best. But, at this point, treating advanced BCC is more experimental and empirical…” — Darrell S. Rigel, MD, MS, FAAD, New York, New York

Schmults recommended presenting a patient to a tumor board if they have a second recurrence. Depending on the case, a multidisciplinary approach to decision-making should involve dermatologists, oncologists, surgeons, endocrinologists, radiologists, and others, she said.

If a tumor board is not available, she advised opening a dialogue with colleagues in surgery and radiation oncology to discuss nonsurgical options or the possible benefit of off-label adjuvant therapies after another surgery. She also noted that there are no FDA-approved adjuvant therapies for BCC with a high risk of recurrence.

Silk emphasized the importance of the radiologist in multidisciplinary care. “In-transit metastases can often be hard to spot on imaging if you are not looking for them,” she noted. “CT scans of head and neck anatomy can be surprisingly hard to read. Radiation oncologists also key team members at a tumor board,” Silk continued. “If there is a recurrence, the radiation oncologist familiar with the patient can tell if it is an in-field recurrence, a marginal recurrence or an out-of-field type of recurrence.”

“Although building a multidisciplinary team is key, Rigel urged dermatologists to remember that they are the patient’s first point of contact. “Even if you are not the physician prescribing the treatment, you have to understand that the patient will what appeared to be a resectable lesion. “However, when the radiologists looked through the image chain, they found that surgery would be over a much larger area than initially thought, which helped steer us away from a surgical approach,” she said.

Instituting a multidisciplinary tumor review board broadens perspectives for patient care and management of advanced basal cell carcinoma.
The anti-PD1 drugs have a 50-50 chance of working...a 50% response rate is really very good in cancer world.”

Chrysalyne Schmults, MD, FAAD, Boston, Massachusetts
Quick TAKES

- The role of redox manipulation in the body’s defense mechanisms could prevent disease onset.
- Thioredoxin reductase 1 destabilizes oxidative regulation in the skin.
- COVID-19–related research into use of a messenger RNA vaccine against external threats and diseases paved the way for this study.

Will a Skin Cancer Vaccine Be the Next Breakthrough?

KEITH LORIA | Staff Correspondent

A vaccine that would stimulate production of a protein critical to the skin’s antioxidant network could help prevent skin cancer, according to a team of investigators from Oregon State University (OSU) College of Pharmacy in Corvallis.

In findings published in the Journal of Investigative Dermatology, the investigators emphasized that redox manipulation is critical for the body’s defense mechanisms.

“We need to be ready and geared to protect ourselves against any types of external threats—environmental toxins—and prevent against disease onset,” said study leader Arup K. Indra, PhD, professor in the Department of Pharmaceutical Sciences, College of Pharmacy, and Department of Biochemistry and Biophysics, College of Science, and Linus Pauling Institute, all at Oregon State University, Corvallis; Department of Dermatology, and OHSU Knight Cancer Institute, both at Oregon Health & Science University, Portland.

Indra noted that his group, which is focused on the prevention and treatment of melanoma, set out to examine the role of redox regulation in this process.

He explained that pigment-producing melanocytes overcome frequent oxidative stress in their physiologic role of protecting the skin against the deleterious effects of solar UV irradiation, thanks to the activity of several endogenous antioxidant systems, including the thioredoxin reductase 1 (TR1) plays an important part.

“We discovered that this protein—TR1—basically plays a significant role in our defense mechanisms in regard to redox regulation,” Indra said. “When you do not have this protein, it increases the sensitivity of our skin cells to solar ultraviolet radiation.”

The investigators concluded that redox regulation by specific endogenous antioxidant proteins is an important factor in controlling survival of the cells that develop aggressive melanoma. “Without specific proteins like TR1, oxidative stress is elevated, which can be a crucial determinant to promote melanoma metastasis,” Indra said. “These results should open up new avenues and new ways to look into the steps to prevent and treat different types of skin cancers.” Vaccination could be one such approach, he added.

The COVID-19 pandemic played a big role in the study, as the success of the Pfizer-BioNTech and Moderna messenger RNA (mRNA) vaccines paved the way for using this type of vaccine against external threats and diseases, he explained.

Indra also noted that UV radiation from the sun leads to oxidative stress, intensifying the risk of skin cancers such as melanoma in patients. “We need to be protected enough to prevent ourselves from excessively suffering from external insults such as harmful UV radiation,” Indra said. “Following uptake of the mRNA into the cell and the cell’s machinery going to work, the cell should be at a high antioxidant capacity and would be able to take care of elevated oxidative stress arising from ultraviolet radiation.”

Investigating antioxidants and their role is nothing new—for more than 4 decades, dietary antioxidants have been studied as a possible source of inexpensive, low-risk agents for cancer prevention—but results have been contradictory. Some findings do suggest the feasibility of a nutritional approach, depending on when and how antioxidants are delivered.

“Without preclinical data from animal models, one cannot demonstrate definitively how this protein even contributes toward our antioxidant defense systems,” Indra said. “Our first demonstration showed that TR1 is a critical defense mechanism for our pigment-producing melanocytes in the skin, despite having other antioxidant proteins present in those same skin cells, which is expected. Just by unplugging this particular protein, you destabilize the process of oxidative regulation in the skin.”

Using a mouse model, the investigators probed TR1’s role in skin cells’ health and stability. The study involved a melanocyte-specific ablation of TR1 in the skin of mice and subsequently challenging the engineered mouse model with UV-B to monitor responses to UV, including DNA damage, oxidative stress, and UV-induced proliferation and migration.

An interesting observation, Indra added, was the significant reduction in the number of melanocytes present in the skin and their proliferation in the absence of TR1. “Furthermore, melanocytes exhibited an elevated level of oxidative stress–induced DNA damage in the form of 8-oxo-2’-deoxyguanosine after acute UVB treatment,” he said. “We also saw an engagement of compensatory antioxidant mechanisms through increased nuclear localization of transcription factor NRF2 [nuclear factor erythroid 2-related factor 2], a key facilitator of cells’ redox signaling.”

These data indicate that melanocytic TR1 positively regulates melanocyte homeostasis and pigmentation during development and protects against UVB-induced oxidative stress.

“We really hope that our defense mechanisms will be boosted, and if we can achieve that, we can create a way to protect against harmful solar UV radiation for ourselves and future generations,” Indra said. “We’re at the tip of the iceberg, but the possibilities of how to prevent different types of disease progression such as cancer by modulating our bodies’ own antioxidant systems is an exciting proposition.”

Reference

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Androgenetic Alopecia Findings Reveal Unmet Treatment Needs

LINDA STOCUM | Associate Editor

Patients with androgenetic alopecia (AGA) want better treatment options, according to survey results presented at both the 2022 Winter Clinical Dermatology Conference and 2022 Maui Derm. The poster highlighted data from an online survey by Follica, Inc, a biotechnology company developing a regenerative platform designed to treat AGA, epithelial aging, and other related conditions.

Conducted in July 2021, the survey was designed to evaluate the attitudes of male patients with AGA regarding hair loss and their potential interest in a novel regenerative treatment approach; the 303 qualified respondents ranged in age from 18 to 49 years. Results showed that patients experienced a negative impact related to AGA, had extensive challenges with existing treatments due primarily to cost and low efficacy, and would welcome a novel in-office treatment for new hair growth.

“Male hair loss is an extremely common complaint among patients in our practice, and unfortunately, we don’t have highly effective ways to address this condition, which has a significant impact on our patients’ well-being,” said Jeffrey Dover, MD, an associate clinical professor of dermatology at Yale School of Medicine in New Haven, Connecticut, and a director and a dermatologist at SkinCare Physicians in Chestnut Hill, Massachusetts, who coauthored the study and is a scientific adviser for Follica. “The survey data clearly corroborate the large unmet need for a new treatment paradigm with the potential to grow new hair safely and successfully over a few months compared [with] years.”

Poster coauthors also included Ken Washenik, MD, clinical assistant professor of dermatology at NYU Grossman School of Medicine in New York, New York, and president of Bosley Medical Group in Beverly Hills, California, and Jonathan Bissett, director of clinical operations at Follica in Boston, Massachusetts.

References
1 Washenik K, Bissett J, Dover J. Unmet treatment needs in AGA and interest in a novel therapeutic approach: survey results in >300 AGA patients. Presented at Maui Derm 2022; January 24-28, 2022; Maui, HI, and virtual.
3 Follica announces poster presentation demonstrating unmet treatment needs in AGA described as an investigational in-office treatment, including a product profile of a device being developed by Follica and a set of before-and-after photos.
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Vitiligo has always been challenging to treat, with a range of options available to patients. Although conservative approaches can be effective, recent advances in surgical techniques have put this treatment approach back in the spotlight.

With a still largely unknown etiology, vitiligo is a common acquired skin disorder thought to be of autoimmune origin, in which destruction of skin melanocytes results in well-demarcated white patches on the body. Vitiligo is classified as nonsegmental and segmental, subgroups further categorized into stable and unstable disease. About 10% to 15% of patients have segmental vitiligo, meaning just 1 segment of the body—eg, half of the face or 1 arm or leg—is affected, and 85% to 90% have the nonsegmental variant.

"Both segmental and nonsegmental vitiligo variants can respond well to topical treatment, light treatment, and surgery, as long as the lesions are not actively growing and the clinician can evaluate before-and-after images to determine whether vitiligo lesions are stable or unstable," said Iltefat Hamzavi, MD, of Hamzavi Dermatology/Dermatology Specialists of Canton, Michigan. He spoke at the 2022 American Academy of Dermatology (AAD) Annual Meeting, held March 25 to 29 in Boston, Massachusetts.

In nonsegmental vitiligo, clinical signs of unstable lesions include confluentlike macules, Köebner phenomenon, and trichrome vitiligo. According to Hamzavi, unstable lesions of either variant are best stabilized with phototherapy; topical; and, sometimes, systemic agents.

Stabilized segmental vitiligo is unlikely to spread, Hamzavi said. Just 10% to 15% of these patients will develop additional lesions, whereas most patients with nonsegmental vitiligo, which can spread anytime, will develop additional lesions. However, segmental vitiligo lesions tend to expand and then stabilize, which can be a challenge to treat because melanocytes won’t come back without replacement therapy, he said.

“The success of surgery in segmental vitiligo ranges anywhere from 70% to 90% of complete repigmentation that lasts more than 7 years,” Hamzavi said. “This is largely due to a different immunology, which is clinically manifested in that the lesions usually do not expand and affect another location. For that patient population, surgery is going to be your best option should topical and phototherapy approaches fail.”

Surgical therapy can also be used in patients with nonsegmental vitiligo with good results; however, because of the increased immunologic state, clinicians must make sure the lesions are stable both before and after the transplant, according to Hamzavi. Patients with nonsegmental vitiligo require medical therapy in addition to surgery to optimize outcomes.

“Segmental and nonsegmental vitiligo both respond to surgery, but the response rates are higher in segmental vitiligo because the immunology is quite unstable,” Hamzavi said. “In my experience, segmental vitiligo really requires a surgical approach, and in most instances, you can get an excellent response.”

Traditional surgical approaches such as punch grafting, split-thickness skin grafting, and suction blister grafting, as well as the melanocyte-keratinocyte transplantation procedure (MKTP) consisting of noncultured epidermal cell suspension, have all proved effective. “MKTP is a type of cellular grafting procedure that has recently been refined and simplified for easier access and implementation. Compared with the more traditional grafting techniques, the response rates with the MKTP approach are much better, often making this the preferred option for patients with vitiligo.”

“Surgery remains a beneficial option for patients with vitiligo,” Ilya Petrov, MD, said. “Modifications simplify the melanocyte-keratinocyte transplantation procedure (MKTP) consisting of noncultured epidermal cell suspension, have all proved effective.”
surgical approach,” said Davinder Parsad, MD, a professor in the Department of Dermatology, Venerology, and Leprology at Postgraduate Institute of Medical Education and Research in Chandigarh, India. He spoke at the same AAD meeting presentation, “Cellular Grafting in Vitiligo: Exciting Options.”

One major advantage of cellular grafting over tissue grafting is that a much larger surface area can be treated in a single procedure. In cellular grafting, a 1-cm graft can cover a 6-cm area, whereas in tissue grafting, the ratio is 1:1. Another advantage of cellular grafting: It provides a better color match with the skin, Parsad said, and can assimilate a more natural repigmentation, increasing patients’ acceptance of this surgical modality.

In the past, cellular grafting was considered very laboratory dependent, requiring dedicated facilities with special trained staff to process tissues. Continued refinements and tweaks to the technique have made the procedure much more approachable for the clinician.

According to Parsad, washing of tissue no longer requires special preparation, simplifying the process. Other modifications include using the required amount of dilution, circumventing the need for centrifugation, and using dermabrasion or a derma roller to prepare recipient areas for application of the cellular suspension.

“Cellular grafting techniques can also be combined with other medical treatment modalities, including the use of phototherapy and topical tacrolimus, helping to ensure a faster, enhanced, and complete repigmentation of the area,” Parsad said.

For patients with stable vitiligo that requires surgical management, cellular grafting has become a first-line therapy. According to Parsad, the process has been simplified and can be performed by any dermatologist who has surgical training and appropriate tools.

“Surgical options have to be part of your armamentarium if you want to treat vitiligo patients. If you only offer phototherapy, topicals, and systemics, you can’t treat patients to complete repigmentation, and there is almost nothing that consistently provides the level of repigmentation that surgery offers in the right patient,” Hamzavi said.

Disclosures
Hamzavi is an investigator for and adviser to Avita Recell. Parsad reported no relevant disclosures.

Reference
In an exclusive interview with *Dermatology Times*, lead abstract author Loren Krueger, MD, assistant professor in the Department of Dermatology, associate program director, residency program, Emory University School of Medicine, Atlanta, Georgia, expanded on findings showcased in the abstract titled “Clinical Decision-Making Bias in Darker Skin Types: A Prospective Survey Study Identifying Diagnostic Bias in Decision to Biopsy.” The abstract catalogued disparities patients of color face in dermatologic care, especially regarding skin cancer and inflammatory disease diagnoses.

Krueger discussed these issues, including unmet needs among patients of color, and initiatives to increase physician diversity in the specialty in her conversation with *Dermatology Times*.

**What was the impetus for your research?**

LK: We know that there are disparities in care for SOC [skin of color] populations, including those relating to skin cancers. Skin cancers may be diagnosed at later stages, and there is increased morbidity for SOC populations. We frequently attribute this to limitations in access to dermatologic care and a lack of awareness of risk. However, we must also understand that bias exists in medicine, and therefore we should know [and identify] any contributions we as dermatologists make to this disparity.

**How did you design the study to investigate possible bias in clinical decision-making?**

LK: There was no perfect way to design this study, but we wanted to know if background skin color plays a role in decision-making. We found images of dermatologic conditions in lighter skin and darker skin and asked dermatologists whether they would biopsy, as well as what they suspected the diagnosis would be. This study design allowed us to compare differences in dermatologists’ decision-making—to explain what those differences were.

The abstract highlights the increases in recommendations of unnecessary biopsy on darker skin.

**FROM THE ABSTRACT:**

Overall, there was an increased propensity to biopsy conditions depicted in darker skin (odds ratio [OR], 1.18; *P* = .054). There was a higher likelihood to biopsy normal variants in darker skin (OR, 2.57; *P* < .0001) but a lower likelihood to biopsy malignant conditions (OR, 0.42; *P* < .0001). The probability of correctly identifying the underlying etiology was lower when depicted in dark skin, including when adjusted for years of dermatology practice (OR, 0.569; *P* < .0001).

What impact do these unneeded procedures have on patients and the health care system?

LK: Biopsies are relatively easy to perform in office and can be very helpful. Of course, we use biopsy when deemed necessary because there is an associated health care cost and a small scar that will develop. Unnecessary biopsies are burdensome to our health care system and our patients.

**In your presentation, you noted that skin cancer is a special area of concern in terms of disparities in decisions such as whether to biopsy. What should dermatologists look for in presentation of skin of color to make a more accurate diagnosis?**

LK: Early detection is key in skin cancer. Often, skin cancer presents differently in SOC populations—for example, in chronic ulcers or discoid lupus. As dermatologists, it is our duty to ensure an appropriate level of suspicion in these cases, even though they are not the typical presentation.

For SOC patients, it is important to note that squamous cell carcinoma [SCC] and basal cell carcinoma [BCC] may present as pigmented. Additionally, SCC is the most common type of skin cancer in Black patients and tends not to occur in sun-exposed areas. Chronic inflammatory or scarring processes have been estimated to account for 20% to 40% of SCC in this population. There is also a markedly higher metastatic potential in the setting of SCC secondary to chronic inflammatory or scarring. Asian patients also have a higher risk of SCCs due to chronic inflammation or scarring.

**How can dermatologists raise awareness in SOC communities to help people recognize the early warning signs of skin cancer?**

LK: SOC communities need more resources and education on warning signs. For example, there has been some effort to promote melanoma screening by hairdressers and nail technicians. Community engagement is key.

**What did your research reveal about decision-making biases in inflammatory conditions such as atopic dermatitis (AD) and psoriasis?**

LK: Our findings showed that participants were more likely to biopsy inflammatory skin conditions in SOC patients. Extrapolating, this may suggest that participants were less comfortable making a clinical diagnosis in background darker skin types and were therefore more likely to biopsy. This finding demonstrates our need for adequate training in all patient populations and phototypes.

**Your presentation noted that “Black patients had 26% lower odds of receiving isotretinoin for acne and 42% lower odds of dupilumab [Dupixent; Sanofi and Regeneron Pharmaceuticals] for AD.” How much of that is the result of bias, and how much is a reflection of the drugs’ cost and availability, patients’ lack of awareness on when to consult a dermatologist, and dermatologists’ knowledge gap in diagnosing and treating these challenging conditions in patients of color?**

LK: The data cited are key as evidence that disparities exist. The disparities are likely multifactorial. These findings demonstrate that there may be biases in decision-making regarding treatment for SOC patients.

**Is telehealth an answer?**

LK: Telehealth certainly has the potential to expand access in both rural and urban settings. Telehealth as a platform does not allow us to eliminate our biases, however. This study used photos, which are commonly the medium in telehealth, and clearly identified our biases.
How can the specialty start to bridge this gap in care? Does it start with medical school training?

LK: Absolutely! I have faith that our specialty is on the way to bridging the gaps, but first they must be identified. There are 2 aspects to address. First, we must make sure that our specialty is diverse and can address the unique needs of every community. This starts even earlier than medical school. We should increase youth interest in STEM [science, technology, engineering, and mathematics] and ensure that our pipeline to dermatology is as inclusive and as equitable as possible. Secondly, all dermatologists, regardless of race or ethnicity, should deliver quality care with cultural humility. Our medical school and residency curricula should reflect this aim.

How can practicing dermatologists learn to better recognize the different presentations of skin diseases on darker phototypes?

LK: Dermatology is such a visual specialty. Images and photos used for teaching should be diverse. Early exposure and training with dermatologists specializing in caring for minority populations and diseases that disproportionately affect minority populations should be available for all trainees. Ultimately, exposure is crucial.

Historically, medical school textbooks and photographic indices have failed to focus on providing diagnosis and manifestation examples for non-White skin. Is this improving?

LK: [It’s] definitely improving, but [there is] still work to be done. A great example of this was the dermatologic manifestations of COVID-19. Despite our field’s recognition that photographic representation of SOC is so important, when the literature on skin findings in COVID-19 was first published, there was a dramatic lack of images in SOC. This was despite the fact that COVID-19 disproportionately affected Black communities.

What other resources are available for physicians and medical students seeking to understand the presentation of skin cancer on people of color?

LK: These resources certainly exist, thankfully. For example, VisualDx [an online learning platform] is intentional about including images in SOC. Additionally, SOC textbooks are available for reference. The AAD [American Academy of Dermatology] website also has a patient-friendly educational link.

What should future studies investigate to improve this situation?

LK: We need more studies on bias as it relates to our diagnostic and therapeutic patterns. Our field should reflect on these to guide our training and future practice. Ultimately, to achieve health equity, we have to ensure that we as dermatologists are doing our part.

Disclosure

Krueger disclosed no relevant conflicts.

Reference

1. Krueger L. Clinical decision-making bias in darker skin types: a prospective survey study identifying diagnostic bias in decision to biopsy. Abstract presented at: 18th Skin of Color Society Scientific Symposium; March 24, 2022; Boston, MA.
**Top Tips for the Practice**

**A** discussion on patient experience and best practices, “60 Tips in 60 Minutes,” kicked off the sessions at the 19th annual Winter Clinical Dermatology Conference held January 14 to 19, 2022, in Koloa, Hawaii.

Session moderator Lawrence J. Green, MD, clinical professor of dermatology, The George Washington University School of Medicine, was joined by Brett Coldiron, MD, a dermatologist from Cincinnati, Ohio; Boni E. Elewski, MD, professor of dermatology, the University of Alabama at Birmingham’s Department of Dermatology; Dee Anna Glaser, MD, professor and interim chairman, director of cosmetic and laser surgery, and director of research at Saint Louis University School of Medicine in St Louis, Missouri; Adelaida A. Hebert, MD, chief of pediatric dermatology at McGovern School of Medicine at The University of Texas Health Science Center at Houston; and Joslyn S. Kirby, MD, MEd, MS, associate professor and vice chair for education, Department of Dermatology, Penn State Health in Hershey, Pennsylvania. Many of their suggestions focused on improving processes and communication in the practice.

**Quick TAKES**

| Dermatologists must disseminate accurate information to their communities. | Interviewing potential office staff virtually requires continued flexibility to align with COVID-19 restrictions. | Making important decisions should be avoided at the end of a long workday. |

Green emphasized the need to disseminate accurate information to communities, in both the clinic and through dermatologists’ online presence. Noting recent steps taken by the FDA’s committee on sunscreen, including updated revisions related to maximum sun protection factor values, active ingredients, and product labeling, Green said it’s important to educate patients on this topic. Through their own websites and social media, dermatologists can help combat the online misinformation related to sunscreens, he said.

“Please go to your social media and educate your patients,” Green urged the audience. “Let’s wait for the FDA to come out with results” about the safety of nonmineral sunscreens. One bill pending in Hawaii would potentially prohibit the sale of nonmineral sunscreens, he noted.

Several panel members said that although the FDA is still updating its guidance, it is important to continue stressing the importance of sunscreen and encourage use of mineral-based sunscreens. One bill pending in Hawaii would potentially prohibit the sale of nonmineral sunscreens, he noted.

Please go to your social media and educate your patients.”

Lawrence J. Green, MD, Washington, DC

**Making important decisions should be avoided at the end of a long workday.**

Coldiron offered tips to ease new employees’ minds, such as installing security measures like safety cameras and promoting a friendly atmosphere with nonpolitical, nonreligious office decor; free Wi-Fi; and family photos: “Show off your kids, not your plaques.”

Kirby expanded on Green’s practice pearls, urging attendees to be mindful of their own limitations in decision-making. “Avoid making important decisions at the end of a long workday, because no matter who we are…we get less good at it as we go along in the day,” she said. For example, she said, when a patient seeks an antibiotic for a skin issue, “you may ask questions of that person who comes in at 8 [A.M.] that maybe, at 11:30 [A.M.] can be challenging to put the same level of that you do in the morning. Being mindful and having insight into who you are throughout the day is important.”

She encouraged staying up-to-date on trends in dermatology by attending continuing education events such as Winter Clinical, listening to podcasts such as Leadership and Loyalty, and reading about office management. These steps will help dermatologists stay at the top of their game while practicing medicine, she said.

**Reference**


**Please go to your social media and educate your patients.”**

Lawrence J. Green, MD, Washington, DC
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Polish Skills to Treat Nail Disorders

ILYA PETROU, MD | Staff Correspondent

Nail disorders such as brittle nails and pincer nails commonly lead patients to seek dermatologic consultation, with each case presenting a particular set of therapeutic challenges for both clinician and patient. A more in-depth understanding of the physiology, biomechanics, and precipitating factors of these disease processes can optimize treatment and management decisions.

“Brittle nails represent the chief complaint in 10% of all medical visits to dermatologists in the United States,” said Dana Stern, MD, assistant clinical professor of dermatology at Mount Sinai in New York, New York, in a presentation at the American Academy of Dermatology (AAD) Annual Meeting in Boston, Massachusetts. “That underscores the need to better address this condition and find meaningful, effective therapies for our patients.”

Brittle nails typically split, flake and crumble, become soft, and lose elasticity, Stern said. The main clinical presentations include onychoschizia, onychorrhexis, superficial granulation of keratin, and worn-down nails. Brittle nails can be either idiopathic or secondary to several causes, including inflammatory nail disorders, infectious, systemic diseases, and medical conditions.

CONCERNS ABOUT BIOTIN

With a recommended daily dose of 10 mg, biotin (vitamin B7) traditionally was touted as a miracle ingredient. However, since the FDA’s 2017 warning that patients taking more than 10 mg daily, biotin can interfere with certain lab tests, including thyroid assays and cardiac markers, clinicians are wary to recommend the supplement as a treatment for brittle nails.

“The impact on cardiac markers is particularly concerning because blood results become difficult to interpret due to the interference phenomenon,” Stern said. “This, combined with the chronic lackluster performance of biotin in my patients, has led me to stop recommending the supplement.”

THE BOLDNDER OPTIONS FOR PINCER NAILS

Pincer nail, another common disorder, characterized by excessive transverse curvature, progressively pinching the nail bed distally; the range of etiologies includes onychomycosis, psoriasis, tumors, cysts, and medications. It can be chronic and recurrent, significantly affecting quality of life. So, surgery is often the optimal choice.

“‘The problem is that conservative options often only provide temporary relief because they may not be addressing the underlying bony causes,’” said Tracey C. Vlahovic, DPM, a clinical professor at Temple University School of Podiatric Medicine in Philladelphia, Pennsylvania at the AAD meeting.

Special bracing and suture techniques have become hot topics in literature, but Vlahovic said these approaches likely will prove suboptimal if any underlying bone deformity isn’t addressed appropriately and may delay surgical correction.

Vlahovic said she prefers the zigzag nail bed flap surgical technique. “The created flap is pulled forward distally to widen the nail bed. This results in a nail bed that is smooth and flat, not too incurvated, and carefully prepared for future nail growth.

“I find that the surgical methods tend to do quite well and are often necessary to appropriately address underlying bony issues. Following surgery, patients are advised to use nail conditioner products that can help ensure the nail grows in healthy.”

For patients who are not candidates for surgery, she said, conservative options can improve symptoms. Using a YAG laser, applying topical tazarotene 0.1% gel, and weighing down the center of the nail with cosmetic resins have proved effective but may provide temporary relief.

“If the dermatologic surgeon isn’t comfortable doing bony procedures, then it is a good idea to consult with a podiatric physician, orthopedic surgeon, or plastic surgeon.....Much of this is in my wheelhouse [as a podiatric surgeon], so this is a good opportunity for our professions to collaborate,” Vlahovic said.
Understanding the Role of JAK Inhibitors

James Q. Del Rosso, DO, FAOCD, FAAD and Neal Bhatia, MD join *Dermatology Times* for the new episodes of DermView: JAK talks. They review the role of Janus Kinase (JAKs) inhibitors in inflammatory diseases, discuss in detail the mechanism of action of JAK inhibitors, specifically topical JAK inhibitors approved for atopic dermatitis, and cover the boxed warning for the topical JAK inhibitor.

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3 Things You Should Know About Psoriasis

Psoriasis is a common immune-mediated inflammatory disease that affects approximately 8 million people in the United States and 125 million worldwide. A complex pathogenesis makes disease management challenging for clinicians and patients. The lack of a clearly defined cause and the absence of a cure, combined with unpredictable symptomology, blur the clinical picture of psoriasis. Recent advances have illuminated critical components of psoriasis pathophysiology and generated targeted therapies with disease-modifying potential. Here are 3 things you should know about psoriasis:

1. Immune dysregulation in psoriasis is multifactorial.

Interactions among various immune cells and keratinocytes lead to the initiation and progression of psoriasis. Extracellular processes like the release of cytokines from immune cells are central to disease pathophysiology. Initially, antigenic stimuli cause activation of dendritic cells and other immune cells in the skin. Dendritic cells produce cytokines like interferon alpha (IFN-α), tumor necrosis factor alpha (TNF-α), and interleukin (IL)-23. These proinflammatory cytokines stimulate activation of various myeloid dendritic cells in the skin. Activated myeloid dendritic cells and macrophages produce more cytokines, including IL-12, IL-20, and IL-23. These processes promote differentiation of
naïve T cells into various effector cells including T helper 17 (Th17) cells stimulated by IL-23 and T helper 1 (Th1) cells stimulated by IL-12. T cells also produce cytokines such as IL-17 and IL-22 that perpetuate the inflammatory cycle and increase clinical symptoms of psoriasis. Activation of the IL-23/IL-17 axis is now considered to be central to the pathogenesis of psoriasis.

Intracellular processes also play a central role in psoriasis pathophysiology. Janus kinase (JAK) and signal transducer and activators of transcription, also called JAK-STATs, are a group of cytoplasmic tyrosine kinases that are activated when a cytokine binds to their receptor. These JAK-STAT proteins transmit signals from the cytoplasm to the nucleus. These signals lead to proliferation and maturation of immune cells, resulting in increased inflammation. For example, IL-23 binding to its receptor on the surface of effector T cells is communicated to the cell interior via JAK-STAT pathways. JAK2 and tyrosine kinase 2 (TYK2) are JAK family proteins critical to signal transduction pathways linked to the IL-23 and IL-12 receptors.

Emerging treatments target immune pathways.

Topical treatments or phototherapy can be sufficient for many patients with mild-to-moderate psoriasis. Recalcitrant or moderate-to-severe disease typically requires consideration of systemic treatment options, which are also recommended when psoriatic arthritis is present. TNF-α inhibitors (eg, etanercept and adalimumab) are among the most common biologics used to treat psoriasis. Blocking TNF-α production can stop the inflammatory cycle, but has limited efficacy and has been associated with serious adverse events. Subsequent drug development was refocused on monoclonal antibodies that target cytokines involved in production of IL and IL receptors. Generally, research indicates that newer biologics targeting the IL-12/23 (eg, ustekinumab) and IL-17 (eg, secukinumab and ixekizumab) axes are more effective than most older biologics and oral agents, with robust efficacy in psoriasis. IL-17 inhibitors, however, can increase risk of mucocutaneous candidiasis and neutropenia as well as trigger or worsen inflammatory bowel disease. IL-23 inhibitors (eg, guselkumab and tildrakizumab) have an overall favorable safety profile and are well tolerated.

Emerging therapeutics include small molecules targeting intracellular drivers of psoriasis. Tofacitinib, an oral JAK inhibitor that targets JAK1 and JAK3, has been approved for use in psoriatic arthritis. Significantly more patients reached at least a 75% reduction in Psoriasis Area and Severity Index scores (PASI 75) compared with placebo after 16 weeks in two randomized controlled trials. Reported adverse events in these patients included herpes zoster and gastric perforation. More recent post hoc analysis found significant improvements in the Nail Psoriasis Severity Index sustained through 52 weeks. As a topical, tofacitinib only resulted in modest improvement of psoriasis symptoms. Tofacitinib is not approved for psoriasis based on clinical efficacy and long-term safety.

Baricitinib is an oral reversible inhibitor of JAK1/2 and has been investigated for the treatment of moderate-to-severe psoriasis. The best outcome of a randomized, double-blind phase 2b study included achievement of PASI 75 by 54% of patients who received 10 mg daily of baricitinib; however, adverse events were more common at this dosage. A link between baricitinib treatment and herpes zoster, gastric perforation and thrombotic events has been observed. Thus, the current treatment landscape emphasizes the need for therapeutics with fewer associated adverse events.

Investigational TYK2 inhibitors are in the treatment pipeline.

TYK2 inhibitors block the intracellular signaling that follows activation of T-cell receptors by cytokines like IL-23. This strategy prevents downstream effects in T
cells, such as production of IL-17, and interrupts the inflammatory cascade. The clinical result is a decrease in the psoriatic plaques that are the end product of the inflammatory pathway. Capitalizing specifically on the TYK2 mechanism may provide novel selective treatment agents without the untoward adverse events seen with JAK inhibition.16 There are 3 key TYK2 inhibitors that have advanced furthest in clinical trials for the treatment of dermatologic autoimmune conditions with the most favorable safety profiles.

“TYK2 inhibitors show promise in interrupting the cycle of psoriasis without many of the adverse effects of the JAK2 inhibitors.”

-April W. Armstrong, MD, MPH

Deucravacitinib is an investigational, oral selective TYK2 inhibitor that is functionally more selective than other tyrosine kinase inhibitors in development for moderate-to-severe psoriasis. This agent uniquely binds to the pseudokinase regulatory domain to act via allosteric inhibition.12 Three phase 3 POETYK trials and an open-label study found that significantly more patients (over 80% at week 24) receiving 6 mg daily of deucravacitinib achieved PASI 75 and a static Physician’s Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) compared with placebo or apremilast.17,18 Results were maintained at week 52. Three serious adverse events occurred in patients receiving treatment, but the most reported adverse events were minor, including nasopharyngitis, headache, nausea, and upper respiratory tract infection.11

Brepocitinib is a potent TYK2/JAK1 inhibitor that is administered orally or topically.19 This agent binds to the active site in the catalytic domain. In a phase 2a trial with 212 patients, the highest PASI 75 response rate occurred in the group receiving 30 mg daily brepoctinib for 12 weeks (86.2%). Treatment-emergent adverse events occurred in 136 patients, including 6 serious adverse events in 5 patients. Thirteen discontinuations in the treatment group occurred due to adverse events.20

Ropsacitinib is an orally formulated TYK2 inhibitor in development for moderate-to-severe psoriasis that binds to the active site in the catalytic domain. Future work is needed to establish the efficacy and safety of these TYK2 targeting agents. These new agents may help close the gap in the management of psoriasis and improve treatment outcomes. Clinicians should have a thorough understanding of the pathophysiology and mechanism of action of available treatment options for psoriasis to identify candidates who may benefit from biologic therapy, including TYK2 inhibitors.

KEY REFERENCES

CME POSTTEST QUESTIONS

1. Which of the following is a true statement about the pathophysiology of psoriasis?
   A. Antigens bind irreversibly to JAK proteins to start the immune response that leads to psoriasis.
   B. Activation of both the JAK- and TYK pathways plays a role in hematopoiesis.
   C. JAK proteins are integral in transmitting intracellular signals to the cell nucleus of T lymphocytes.
   D. JAK proteins are located on the external surface of the cell membrane of T cells and facilitate the transfer of signals through the cell membrane.

2. In the phase 3 studies POETYK-PSO-1 and POETYK-PSO-2, which compared deucravacitinib and apremilast with placebo in patients with psoriasis, which of the following is true?
   A. Dianhea and nausea were the most common adverse events recorded for deucravacitinib and apremilast in both trials.
   B. Deucravacitinib was equal to apremilast in both trials for the static Physician’s Global Assessment 0/1 score at week 16 through week 24.
   C. Over 80% of deucravacitinib patients who achieved Psoriasis Area and Severity Index (PASI) 75 at week 24 and continued treatment maintained a PASI 75 response at week 52 in both trials.
   D. Significantly greater improvement from baseline in Psoriasis Symptom and Sign Diary symptom scores was observed for deucravacitinib compared with apremilast at week 16 in both trials, but not at week 24 or greater.

To learn more about this topic, including information on the use of TYK2 inhibition in the treatment of psoriasis, go to gotoper.com/mauiTKY-act
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