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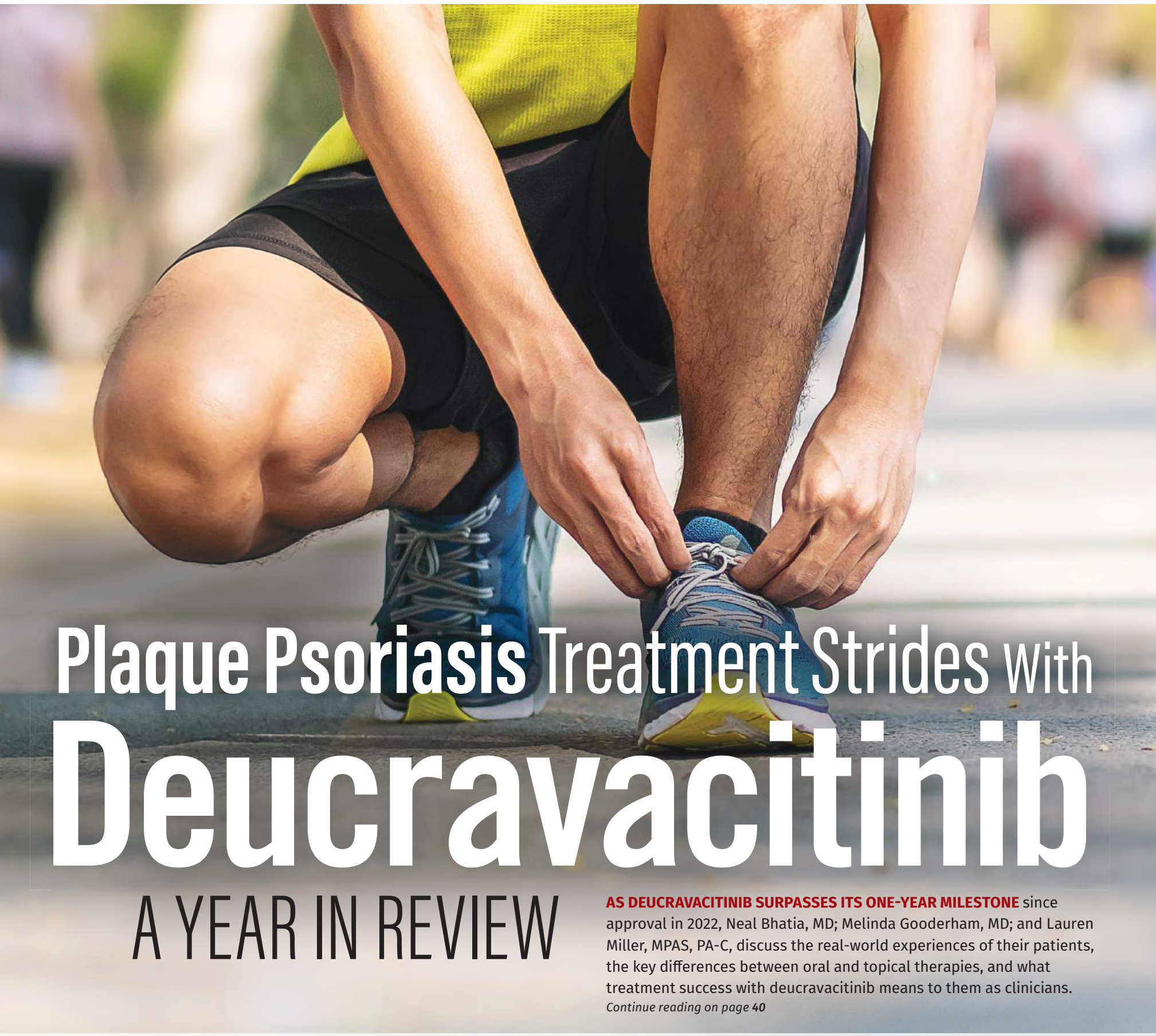

Plaque Psoriasis Treatment Strides With Deucravacitinib

A YEAR IN REVIEW

AS DEUCRAVACITINIB SURPASSES ITS ONE-YEAR MILESTONE since approval in 2022, Neal Bhatia, MD; Melinda Gooderham, MD; and Lauren Miller, MPAS, PA-C, discuss the real-world experiences of their patients, the key differences between oral and topical therapies, and what treatment success with deucravacitinib means to them as clinicians.

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INDICATION[1]

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.

IMPORTANT SAFETY INFORMATION[1]

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 TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

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

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of 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.

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.[1]

FOR UNCONTROLLED AD PATIENTS

DISRUPT EXPECTATIONS

#1 PRESCRIBED oral JAK inhibitor for AD[2*]

~4 years of safety data in AD[3]

RAPID RELIEF

- EASI 75 results as early as Week 2 and reduction of worst pruritus NRS ≥4 measured at Week 16 with results observed at 2 days after first dose[1,4]
- No to little itch (NRS 0/1) rates measured at Week 16[5,6]

DURABLE CONTROL

- Co-primary endpoints EASI 75 and vIGA 0/1 controlled at Week 16[1]
- Response rates for skin & itch observed up to 52 weeks[5]

ROBUST RESPONSE

- 90% skin improvement (EASI 90) measured at Week 16[1]

LEARN MORE AT RINVOQHCP.COM/AD

In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, 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 that 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.

Please see additional Important Safety Information on the following pages of this advertisement.

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

IMPORTANT SAFETY INFORMATION[1] (cont'd)

RINVOQ® upadacitinib

ONE PILL, ONCE-DAILY

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

GASTROINTESTINAL PERFORATIONS
Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES
Neutropenia
Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia
Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

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

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

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

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

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

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

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

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

Dosage Forms and Strengths: RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

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

EASI 75=improvement of at least 75% in lesion extent and severity. EASI 90=improvement of at least 90% in lesion extent and severity. vIGA 0/1=clear or almost clear with at least 2 grades of reduction from baseline. Worst pruritus NRS ≥4=improvement (reduction) in worst pruritus NRS ≥4 points from baseline.

*As of 7/2022. Source: Integrated Symphony Health (PatientSource) and IQVIA (NSP).

AD=atopic dermatitis; EASI=Eczema Area and Severity Index; NRS=numerical rating score; vIGA=Validated Investigator Global Assessment.

References: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc.; 2022. **2.** DOF [Data on File]. ABVRRTI74605. **3.** DOF [Data on File]. ABVRRTI74922. **4.** Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. 2021;397(10290):2151-2168. **5.** Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the Measure Up 1 and Measure Up 2 randomized clinical trials. *JAMA Dermatol*. 2022;158(4):404-413. **6.** Reich K, Silverberg JI, de Bruin-Weller MS, et al. Deep and rapid response on skin clearance and patient-reported outcome measures with upadacitinib with or without topical corticosteroids in moderate to severe atopic dermatitis: results from three phase 3 studies (Measure Up 1, Measure Up 2, and AD Up). Poster presented at EADV 2021.

abbvie

RINVOQ® (RIN-VOKE) (upadacitinib) extended-release tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Adverse Reactions]*. 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, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with RINVOQ 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 RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

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

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 RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Atopic Dermatitis

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.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.

Ankylosing Spondylitis

RINVOQ is indicated for the treatment of adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Non-radiographic Axial Spondyloarthritis

RINVOQ is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

CONTRAINDICATIONS

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- 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 RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ. RINVOQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

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

Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

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

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

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

Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

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

Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. Avoid RINVOQ in patients that may be at increased risk of thrombosis.

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy *[see Adverse Reactions]*.

Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ.

Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

Vaccinations

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

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Mortality *[see Warnings and Precautions]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Abnormalities *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 1: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials

Adverse Reaction	Placebo	RINVOQ 15 mg
	n=1042 (%)	n=1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancies

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V,

decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical trials representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the two Phase 3 trials, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled trials were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were ≥1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

Adverse Reactions in Patients with Atopic Dermatitis

Three Phase 3 (AD-1, AD-2, and AD-3) and one Phase 2b (AD-4) randomized, double-blind, placebo-controlled, multicenter trials evaluated the safety of RINVOQ in patients with moderate-to-severe atopic dermatitis. The majority of patients were White (68%) and male (57%). The mean age was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. In these 4 trials, 2612 patients were treated with RINVOQ 15 mg or 30 mg orally once daily, with or without concomitant topical corticosteroids (TCS).

In the Phase 3 clinical trials (AD-1, AD-2, and AD-3), a total of 1239 patients received RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received RINVOQ 30 mg, of whom 826 were exposed for at least one year.

Trials AD-1, AD-2, and AD-4 compared the safety of RINVOQ monotherapy to placebo through Week 16. Trial AD-3 compared the safety of RINVOQ + TCS to placebo + TCS through Week 16.

Weeks 0 to 16 (Trials AD-1 to AD-4)

In RINVOQ trials with and without TCS (Trials AD-1, 2, 3 and 4) through Week 16, the proportion of patients who discontinued treatment because of adverse reactions in the RINVOQ 15 mg, 30 mg and placebo groups were 2.3%, 2.9% and 3.8%, respectively. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the RINVOQ 15 mg or 30 mg groups during the first 16 weeks of treatment.

Table 2: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg

Adverse Reaction	Placebo	RINVOQ 15 mg	RINVOQ 30 mg
	n=902 (%)	n=899 (%)	n=906 (%)
Upper respiratory tract infection (URTI)*	17	23	25
Acne**	2	10	16
Herpes simplex***	2	4	8
Headache	4	6	6
Increased blood creatine phosphokinase	2	5	6
Cough	1	3	3
Hypersensitivity****	2	2	3
Folliculitis	1	2	3
Nausea	1	3	3
Abdominal pain*****	1	3	2
Pyrexia	1	2	2
Increased Weight	1	2	2
Herpes zoster******	1	2	2
Influenza	<1	2	2
Fatigue	1	1	2
Neutropenia	<1	1	2
Myalgia	1	1	2
Influenza like illness	1	1	2

* Includes: laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
** Includes: acne and dermatitis acneiform
*** Includes: genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
**** Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalized, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, urticaria
***** Includes abdominal pain and abdominal pain upper
****** Includes herpes zoster and varicella

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 16 included anemia, oral candidiasis, pneumonia, and the adverse event of retinal detachment.

The safety profile of RINVOQ through Week 52 was generally consistent with the safety profile observed at Week 16.

Overall, the safety profile observed in patients with AD treated with RINVOQ was similar to the safety profile in patients with RA. Other specific adverse reactions that were reported in patients with AD included eczema herpeticum/Kaposi's varicelliform eruption.

Eczema Herpeticum/Kaposi's Varicelliform Eruption

Placebo-controlled Period (16 weeks): Eczema herpeticum was reported in 4 patients (1.6 per 100 patient-years) treated with placebo, 6 patients (2.2 per 100 patient-years) treated with RINVOQ 15 mg and 7 patients (2.6 per 100 patient-years) treated with RINVOQ 30 mg.

12-Month Exposure (Weeks 0 to 52): Eczema herpeticum was reported in 18 patients (1.6 per 100 patient-years) treated with RINVOQ 15 mg and 17 patients (1.5 per 100 patient-years) treated with RINVOQ 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg once daily and 251 patients received RINVOQ 30 mg once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 3 and 4, respectively.

Table 3. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N= 378 (%)	N = 719 (%)
Upper respiratory tract infection*	7	9
Acne*	1	6
Increased blood creatine phosphokinase	1	5
Neutropenia*	<1	5
Rash*	1	4
Elevated liver enzymes**	2	3
Lymphopenia*	1	3
Folliculitis	1	2
Herpes simplex*	<1	2

* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis.

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

Table 4. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	n = 245 (%)	n = 250 (%)	n = 251 (%)
Upper respiratory tract infection*	18	16	20
Increased blood creatine phosphokinase	2	6	8
Neutropenia*	2	3	6
Elevated liver enzymes**	1	6	4
Rash*	4	5	5
Herpes zoster	0	4	4
Folliculitis	2	2	4
Hypercholesterolemia*	1	2	4
Influenza	1	3	3
Herpes simplex*	1	2	3
Lymphopenia*	2	3	2
Hyperlipidemia*	0	2	2

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily
* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

Specific Adverse Reactions

Serious Infections

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (6.3 per 100 patient-years) treated with placebo, 8 patients (4.5 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (3.1 per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 0.8% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 0.8% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

Adverse Reactions in Patients with Ankylosing Spondylitis

A total of 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical trials representing 577.3 patient-years of exposure, of whom 220 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis and psoriatic arthritis. During the 14-week placebo-controlled period in Trial AS-I, the frequency of headache was 5.4% with RINVOQ 15 mg and 2.1% with placebo. During the 14-week placebo-controlled period in Trial AS-II, the frequency of headache was 3.3% with RINVOQ 15 mg and 1.4% with placebo.

Adverse Reactions in Patients with Non-radiographic Axial Spondyloarthritis

A total of 187 patients with non-radiographic axial spondyloarthritis were treated with RINVOQ 15 mg in the clinical trial representing 116.6 patient-years of exposure, of whom 31 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active non-radiographic axial spondyloarthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole and clarithromycin), which may increase the risk of RINVOQ adverse reactions. Monitor patients closely for adverse reactions when co-administering RINVOQ 15 mg once daily with strong CYP3A4 inhibitors.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg dose, 0.8 and 7.6 times the 30 mg dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MHRD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity (*see Data).*

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Report pregnancies to the AbbVie Inc.'s Adverse Event reporting line at 1-888-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg dose, 0.9 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg dose, 0.15 times the 30 mg dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg dose, 7.6 times the 30 mg dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg dose, 1.1 times the 30 mg dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations].*

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations].* Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

Pediatric Use

Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis have not been established.

Atopic Dermatitis

The safety and effectiveness of RINVOQ in pediatric patients 12 years of age and older weighing at least 40 kg with atopic dermatitis have been established. A total of 344 pediatric patients aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across three trials (AD-1, AD-2 and AD-3) to receive either RINVOQ 15 mg (N=114) or 30 mg (N=114) or matching placebo (N=116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the pediatric patients and adults. The adverse reaction profile in the pediatric patients was similar to the adults *[see Adverse Reactions].*

The safety and effectiveness of RINVOQ in pediatric patients less than 12 years of age with atopic dermatitis have not been established.

Ulcerative Colitis

The safety and effectiveness of RINVOQ in pediatric patients with ulcerative colitis have not been established.

Geriatric Use

Rheumatoid Arthritis and Psoriatic Arthritis

Of the 4381 patients treated in the five clinical trials, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical trials, a total of 274 patients were 65 years of age or older, including 34 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in patients 65 years of age and older.

Atopic Dermatitis

Of the 2583 patients treated in the three Phase 3 clinical trials, a total of 120 patients with atopic dermatitis were 65 years of age or older, including 6 patients 75 years of age. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of serious infections and malignancies in those patients 65 years of age or older in the 30 mg dosing group in the long-term trials.

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

Ankylosing Spondylitis

Of the 607 patients treated in the controlled clinical trials, a total of 32 patients with ankylosing spondylitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ankylosing spondylitis to determine whether they respond differently from younger adult patients.

Non-radiographic Axial Spondyloarthritis

Of the 313 patients treated in a phase 3 clinical trial, a total of 9 patients with non-radiographic axial spondyloarthritis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with non-radiographic axial spondyloarthritis to determine whether they respond differently from younger adult patients.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis, no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2).

For patients with atopic dermatitis, the maximum recommended dosage is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis, the recommended dosage for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment.

RINVOQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73m^2). Use in patients with atopic dermatitis or ulcerative colitis with end stage renal disease is not recommended.

Hepatic Impairment

The use of RINVOQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis, the recommended dosage for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance.

PATIENT COUNSELING INFORMATION

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

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions].*

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions].*

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

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

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions].*

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions].*

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions].*

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDS or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions].*

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions]*.

Laboratory Abnormalities

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

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations]*.

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients not to chew, crush, or split RINVOQ tablets.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, USA

Ref: 20071756 Revised: October 2022

LAB-8208 **MASTER**

US-RNQD-220607

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A Spotlight on Innovations and Considerations

Innovation is one of the strongest core values at MJH Life Sciences, and spotlighting advances in dermatologic care remains a top priority for the *Dermatology Times*® team. In this month's issue, we take an in-depth look at the 1-year anniversary of the approval of deucravacitinib (Sotyktu; Bristol Myers Squibb) for the treatment of adults with moderate to severe plaque psoriasis. A panel of clinicians delves into the drug's efficacy, its pros and cons, what makes it different from other psoriasis therapies, and special considerations for patients with skin of color. We are also thrilled to share a psoriasis supplement focusing on psoriasis treatment, advances, and clinical resources to best serve individuals with skin of color and other underserved populations.

On the heels of Labor Day weekend, we discuss how skin cancer can have a lasting impact on workers in certain career fields or those with heroic roles in historic events. Discover how aircrews are more susceptible to skin cancers and how dermatologic care amid their busy schedules is critical. There is also a look at areas of the body on which rescue workers from the September 11, 2001, attacks showed a higher risk of melanoma years later. These are also insightful considerations for treating patients who are firefighters.

This is an issue packed with the latest research, monthly columns to strengthen your practice management, and considerations on a variety of topics to help dermatologists, nurse practitioners, physician assistants, and aspiring clinicians enhance their professional experiences.

Do not miss a moment of new data, pearls, interviews, videos, and podcasts with leaders in the field. Subscribe to *Dermatology Times* e-newsletters, follow us on social media, and email us at DTeditors@mmhgroup.com to share your insights. ■

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Our article "Improving the Quality of Life for Patients With Albinism" in the July 2023 issue showed a mislabeled headshot of Amor Khachemoune, MD. The photo of a large invasive squamous cell carcinoma on a patient with albinism was provided by Khachemoune's colleague Ibrahima Traoré, MD, PgDip, MSc, leading dermatologist in Conakry, Guinea.

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BPA WORLDWIDE

Cover Image: Jo Panuwat D/Stock.Adobe.com

Taking a Proactive Approach to Aging

The concept of aging is complex, multifactorial, and poorly understood. In dermatology, we deal with the most obvious signs of aging related to skin appearance. Every day, the mirror documents skin aging in detail for all. The problem is that we have no treatments for aging. Why? Because, according to the US Food and Drug Administration, aging is not a disease. I would argue that aging is the culmination of all disease processes. Coronary artery disease is aging of the heart. Osteoporosis is aging of the bones. Dementia is aging of the brain. Diabetes is aging of the pancreas. Most persons develop a constellation of systemic issues over a lifetime, which are collective aging of the organism. However, these are the end stages of aging, where disease is present. What about the early stages of aging, where prevention is possible and disease could be averted? Medicine would be a different undertaking if patients were administered preventive procedures and drugs.

Last week, I saw a healthy male patient aged 45 years who noted in his medical history that he had a grandfather and father who both had developed severe macular degeneration. I asked him about his diet, and he related that he largely ate rice and chicken, neither of which contains the carotenoid lutein, which is important in preventing oxidative damage to the retina. I mentioned that he should increase his intake of carotenoid-containing foods including tomatoes, watermelon, carrots, and egg yolks or he would probably develop macular degeneration. Developing novel tests and devices that address body deficiencies early, especially in the realm of vitamins and antioxidants, would optimize nutrition and health. We know what the minimum recommended daily allowance is based on required food labeling, but we do not know what the sex- and age-adjusted optimum recommended daily allowance might be. We no longer see patients with scurvy from vitamin C deficiency in dermatology, so the minimum daily allowance recommendations are working, but we do not know what the optimum vitamin C intake is for preventing oxidative damage that results in the skin prewrinkle. Imagine if we could treat the prewrinkle. Dermal collagen loss could be addressed early in the aging process and oral antioxidant intake and topical antioxidant use could more effectively intervene. Evaluating vitamin C levels is essential because vitamin C supplies vitamin E with an electron to quench reactive oxygen species on a continuous basis when exposed to UV radiation.

We need to make aging of body organs a disease so that prescription and OTC drugs and tests can be created to address the prefunctionality loss. The delivery of medicine would be much more effective at the predisease state and the outcomes far superior, but there needs to be a regulatory approval route for devices and drugs that address the aging organ prior to disease onset. Medical costs would plummet as humans reached maturity with fewer signs and symptoms of aging, which represent disease. Because dermatology is the most visual specialty in medicine, treating the predisease state is possible. Further, dermatology allows easy assessment as to the success of the treatment. Creating a pathway for approval of prescription and OTC drugs and devices addressing the predisease state would propel dermatology into the next generation of therapy; however, we first must recognize that aging is a disease.

Zoe Diana Draelos, MD, is a consulting professor of dermatology at Duke University School of Medicine in Durham, North Carolina, and editor in chief of *Dermatology Times*.

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ZORYVE®
(roflumilast) cream 0.3%

In DERMIS-1 and DERMIS-2, ~40% of patients achieved IGA Success and ~70% of patients achieved I-IGA Success at Week 8.[1]

DERMIS-1 and DERMIS-2 were identical Phase 3 randomized, parallel, double-blind, vehicle-controlled, multicenter studies that evaluated ZORYVE over 8 weeks as a once-daily, topical treatment for plaque psoriasis. Subjects (N=881) were randomized 2:1 to receive ZORYVE cream 0.3% (n=576) or vehicle (n=305) applied once daily for 8 weeks. Eligibility criteria included a diagnosis of mild, moderate, or severe plaque psoriasis and an affected BSA of 2% to 20%. Primary endpoint was IGA Success at Week 8 and key secondary endpoint was I-IGA Success at Week 8.[1]

IGA Success was defined as a score of Clear (0) or Almost Clear (1) and a ≥2-grade improvement from baseline. I-IGA Success was defined as a score of Clear (0) or Almost Clear (1) and ≥2-grade improvement from baseline.

ZORYVE is not for ophthalmic, oral, or intravaginal use.

BSA = Body Surface Area, IGA = Investigator's Global Assessment, I-IGA = Intertriginous-IGA

FOR AGE 12+

Effective. Everywhere. Easy.[1]

A once-daily, steroid-free cream with the **power to clear elbows and knees**, and the **gentleness for face and folds**.[1,2]

See the results at zoryvehcp.com

Actor portrayal

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

Please see brief summary of full Prescribing Information for ZORYVE on the following page.

References: 1. ZORVYE®. Prescribing information. Arcutis Biotherapeutics, Inc; 2022. **2.** Data on File. Arcutis Biotherapeutics, Inc.

ARCUTIS® BIOTHERAPEUTICS

COM-ARQ-151-2100003 v4.0 02/2023

Brief Summary of Prescribing Information for ZORYVE™ (roflumilast) cream, for topical use. See package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Apply ZORYVE to affected areas once daily and rub in completely. Wash hands after application, unless ZORYVE is for treatment of the hands.

ZORYVE is for topical use only and not for ophthalmic, oral, or intravaginal use.

CONTRAINDICATIONS

The use of ZORYVE is contraindicated in the following condition:

- Moderate to severe liver impairment (Child-Pugh B or C)

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

The median age was 47 years (range 6 to 88). The majority of the subjects were male (64%) and White (82%). The median body surface area (BSA) affected was 5.5% (range 2% to 20%).

The proportion of subjects who discontinued treatment due to adverse reaction was 1.0% for subjects treated with ZORYVE and 1.3% for subjects treated with vehicle. The most common adverse reactions that led to discontinuation of ZORYVE was application site urticaria (0.3%).

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

Labor and delivery

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

Data

Animal data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

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

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral doses of 0.8 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

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

Lactation

Risk Summary

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

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

Clinical Considerations

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

Data

Animal data

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

Pediatric Use

The safety and effectiveness of ZORYVE have been established in pediatric patients ages 12 years and older for the treatment of plaque psoriasis. Use of ZORYVE in this age group is supported by data from two 8-week vehicle-controlled safety and efficacy trials which included 14 adolescent patients aged 12 to 17 years, of whom 8 received ZORYVE. Eighteen adolescent patients were treated with ZORYVE in open-label trials of 2- and 24-weeks duration. The adverse reaction profile was similar to that observed in adults.

The safety and effectiveness of ZORYVE in pediatric patients below the age of 12 years have not been established.

Geriatric Use

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

Hepatic Impairment

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

PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information).

08/2022

Maximize Device Options for Acne and Acne Scarring

Heather Raglin, MS, Editor

Scarring exacerbates the emotional and psychological effects of acne.[1,2] In a study of patients 15 years and older, acne had a significant effect on emotions, daily and social activities, study and work, and interpersonal relationships.[1] The scars left by acne can create issues with body image, self-esteem, and overall quality of life.[2] Treatments including lasers and microneedling are becoming more popular for treating these skin conditions with positive results for patients.

Treatments for Acne

Several laser and light-based therapies have been developed for treating acne. Blue and red light therapy have been used for years to successfully treat acne and improve skin quality. "Blue light harnesses the power of the natural porphyrins in the skin to kill *C acnes* [*Cutibacterium acnes,* formerly *Propionibacterium acnes*], whereas red light has anti-inflammatory effects. If we take this a step further and consider using either blue or red light as part of a PDT [photodynamic therapy] treatment, we know from studies and case reports that PDT has the potential to be a potent acne treatment, even a cure," Ted Lain, MD, MBA, board-certified dermatologist and chief medical officer with Sanova Dermatology in Austin, Texas, told *Dermatology Times*. He added, "However, the most effective, durable responses using PDT for inflammatory acne require a 3-hour incubation with either Ameluz [aminolevulinic acid hydrochloride] or Levulan [aminolevulinic acid HCl], followed by a very painful illumination. That, coupled with severe posttreatment local site reactions, limits the utility of this treatment."

"PDT [photodynamic therapy] has the potential to be a potent acne treatment, even a cure,"

Ted Lain, MD, MBA

A recent advance in the treatment of acne is the 1726-nm laser, which treats mild to severe acne with minimal pain and discomfort for the patient.[3] Combining the laser therapy with optimal contact cooling creates a temperature increase isolated to the sebaceous gland, which maximizes damage to the gland while keeping surrounding skin intact.[3]

Devices are effective for adults and adolescents. "I think the device treatment options work well in both patient populations and offer this [1726-nm laser] alongside more traditional medical treatments during a patient visit," Lain said.

Acne treatments can benefit a patient's overall well-being. "With any laser or device treatment for acne, the pros usually include effective treatment without the need for oral or topical therapies, improvement that enhances over time, and little to no downtime. The cons include no payer coverage and, like any treatment, lack of uniform response [among] patients," Lain explained.

Treatments for Acne Scarring

Factors such as the type of acne scarring and physician expertise can play a role in which treatment will be most effective for a patient. In many studies, microneedling, also known as percutaneous collagen induction or collagen induction therapy, has been effective in treating acne scarring. "Microneedling does shine as a treatment for acne scarring, particularly in the adolescent to young adult population," Lain said.

In studies, microneedling has been used alone or in combination with other therapies, such as peels, vitamin C, and platelet-rich plasma, exhibiting effectiveness and resulting in patient satisfaction.[4]

"Microneedling has been shown to improve scars of various etiologies and striae," Monica K. Li, MD, double board-certified dermatologist and clinical assistant professor with the Department of Dermatology and Skin Sciences at the University of British Columbia in Canada, told *Dermatology Times*. She added, "Microneedling is an increasingly popular treatment worldwide, for all skin types and tones. It is a treatment that is relatively easy to integrate into clinical practice given the cost of the device for the dermatologist and cost of the treatment for patients."

In a randomized, split-face, placebo-controlled trial, 15 patients with varying types of acne scarring received 3 needling treatments at 2-week intervals using an MTS Roller, either CR10 (1.0 mm) or CR20 (2.0 mm). At 3 months, the mean scar scores based on the quantitative global scarring grading system of treated scars were nominally lower than at baseline in the treatment group. At 6 months, the mean scar scores of scars treated with microneedling were significantly lower than at baseline (mean difference, 3.4; 95% CI, 0.2-6.5; $P = .03$). Mean scar scores did not vary significantly from baseline at 3 or 6 months in the control group.[4]

Li added that precautions need to be taken when using microneedling, including adjusting needle depths to the specific skin location and thickness. "An example would be the need for deeper needle penetration for thick sebaceous skin compared to thin periocular skin," she said. Li also cautioned to avoid microneedling on tanned skin or skin with recent sun exposure to avoid postprocedure dyspigmentation.

"[Microneedling] is a treatment that is relatively easy to integrate into clinical practice given the cost of the device for the dermatologist and cost of the treatment for patients."

Monica K. Li, MD

Another treatment option is fractional lasers (FLs). More recently, the fractional picosecond laser has been used with success, offering lower postinflammatory hyperpigmentation and pain scores than the FL.[5]

Studies of microdermabrasion to treat acne scarring have shown that it does not provide satisfactory results. In a study, only 1 patient exhibited good results from microdermabrasion, and no participants had very good results.[4]

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skin cancer

World Trade Center 9/11 Rescue Workers Show Higher Risk of Melanoma

Heather Raglin,MS, Editor

RESEARCHERS WANTED TO BETTER UNDERSTAND the risk of developing malignant melanoma for rescue workers exposed to the toxins released due to the September 11, 2001, attacks at the World Trade Center (WTC) in New York, New York.[1] Beyond the immediate fatalities, the destruction released toxic substances such as asbestos, benzene, chromium, dioxins, and polychlorinated biphenyls.[1,2] From the morning of the attacks and continuing 9 or more months afterward, an estimated 90,000 first responders and rescue, recovery, and cleanup workers were at the site.[2]

Amy Spizuoco, DO, FAOCD, board-certified dermatologist, dermatopathologist, associate clinical instructor in the Department of Dermatology at the Icahn School of Medicine at Mount Sinai in New York, New York, and *Dermatology Times* Editorial Advisory Board member, said, "Studies have shown 9/11 rescue workers had an increased rate of malignant melanoma between 2005 and 2015 compared [with the] New York State [NYS] general population. Typically, malignant melanoma is associated with UV radiation; however, some studies show a statistically significant increase in 9/11 rescue workers."

Three cohorts of WTC-exposed rescue and recovery workers—the Fire Department of the City of New York (FDNY), World Trade Center Health Program General Responder Cohort, and World Trade Center Health Registry—have shown an increased incidence of malignant melanoma.[1,2] Researchers wanted to further explore the time between environmental carcinogen exposure and the emergence of a higher incidence of melanoma among non-Hispanic white rescue workers.[1] Regarding WTC exposure and cancer, Brackbill et al noted, "In general, the results have been consistent, with effect estimates for all cancers from the most recent studies ranging from 6% to 14% in excess of background rates."[2]

Researchers analyzed the incidence of malignant melanoma among 44,540 WTC rescue workers and found 247 cases of melanoma in 241 individuals between March 12, 2002, and December 31, 2015, with 491,492 person-years of follow-up. Using the population of NYS as a reference population, researchers identified 46,233 cases of melanoma with 134,922,302 person-years of follow-up.[1]

Pooling data from 3 cohorts offers several advantages, including an increased sample size resulting in an improvement in statistical power and increasing the heterogeneity of occupations, which offers a greater degree of generalizability of the findings. The pooled data also has its disadvantages, particularly the level of detail provided on self-reported exposure.[2]

Age at diagnosis ranged from 28 to 88 years, with the mean age being 55.9 years (SD, 11.5). The mean time from the 9/11 attacks to diagnosis of melanoma was 9.3 years (IQR, 6.5-12.1). Of the cases of melanoma, 5.8% (n = 14) died during the follow-up period compared with 3.1% of persons without melanoma. WTC rescue workers had a higher proportion of localized tumors (75.7%), a lower proportion of regional tumors (5.7%), and a similar proportion of distant tumors (4.5%) compared with the NYS population (71.4%, 9.3%, and 4.2%, respectively).

Most of the tumors on rescue workers were on the trunk (n = 112, 45.3%), followed by the upper limb or shoulder (n = 45, 18.2%), and the lower limb or hip (n= 32, 13%). Most melanomas had an unspecified histological subtype (70%), followed by superficial spreading melanoma (18.6%), nodular melanoma (4.5%), and lentigo maligna melanomas (2.4%). The remaining histological

A **32% increased hazard** was observed among those who **worked on the WTC pile** compared with that observed among those who did not.

Firefighter Montreal/Stock.Adobe.com

subtypes each had fewer than 5 cases. According to Boffetta et al, "The incidence of melanoma among the combined cohort was greater than that of NYS throughout the entire study period and increased with follow-up."[1] Researchers continued, "In our analysis, which only evaluated localized tumors as the outcome, we observed no change points and an increased hazard compared with those in NYS (HR, 1.36; 95% CI, 1.18-1.57)."[1]

Researchers did not observe an increase in melanoma rates among WTC workers compared to NYS prior to 2005 but did see a 34% increase in risk from 2005 to 2015. They suggest this difference could be due to the small number of cases that occurred from 2002 to 2004, and to an overrepresentation of FDNY cohort members in the early period of follow-up.

Based on an internal analysis using those with the least exposure as the referent category, authors observed a change point in 2009 with those workers who were at the site in the first week following the attacks showing a higher risk of melanoma. An external analysis of those who worked at the WTC site any time between September 11, 2001, and June 30, 2002, showed a change point in 2004. According to Boffetta et al, "In addition, a 32% increased hazard was observed among those who worked on the WTC pile compared with that observed among those who did not; however, no change points were detected."[1]

The main strength of the study was "that there was greater statistical power than previous analyses of WTC rescue and recovery workers, leading to a detailed assessment of temporal aspects of the association and the ability to conduct internal dose-response analyses. In addition, by including 13 different states in the linkages of the cohort to central cancer registries, we were able to cover 93% of the addresses of the 44,540-member study population."[1]

Other factors such as sun exposure in childhood, as well as environmental and occupational exposures that occurred outside of the WTC effort, may have contributed to increased rates of melanoma. Authors also suggest that an increase in monitoring of skin changes might account for a portion of the higher incidence among WTC workers but does not explain the 36% increase in risk over the study period. Combining the factors of WTC exposures, sun exposures, increased skin monitoring, and cumulative occupational exposures may have contributed to an earlier onset of melanoma.[1] The study results showed a higher risk of developing melanoma among WTC rescue workers and Boffetta et al suggest that continued follow-up of the population is warranted.

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Tumor locations on rescue workers

The incidence of melanoma among the combined cohort was **greater than that of NYS throughout the entire study period** and increased with follow-up.

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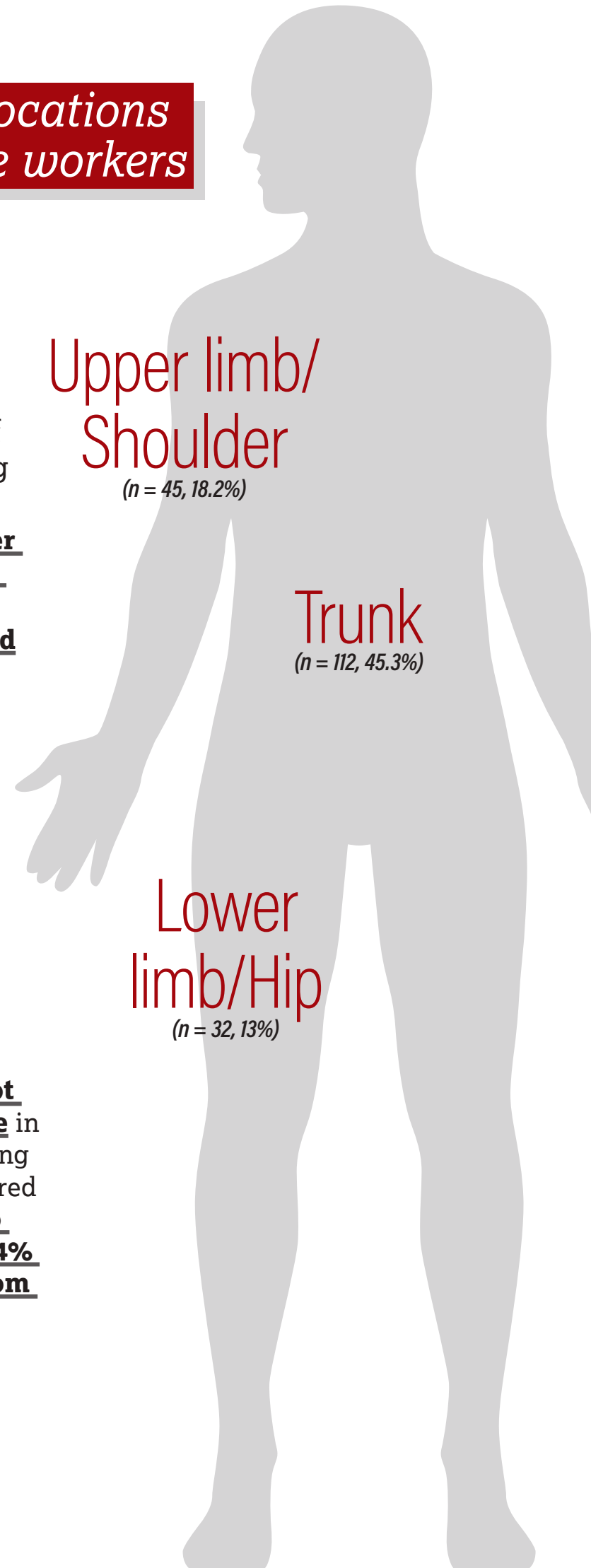

Guidelines for Surgical Treatment of Early-Stage Vulvar SCC

Kaitlyn Bader, Senior Editor

A recent literature review[1] published in the *International Journal of Women's Dermatology* examined gynecology guidelines for the management of vulvar squamous cell carcinomas (vSCCs) to better inform dermatologic surgeons of when and why to escalate patient care. From their review, Rao et al recommended that dermatologists should be familiar with the guidelines used by other specialists treating vSCC due to its morbidity in this region of the body.

"Dermatologic surgeons often play an important role in the treatment of these malignancies and therefore need to understand the difference in the gynecology-oncology guidelines compared to more commonly treated tumors in other locations. In particular, lymph node biopsy or radical vulvectomy is recommended for many of these SCCs. Dermatologic surgeons should be aware of these guidelines to inform their clinical plans," said study author Elizabeth Rao, a fourth-year medical student in the department of dermatology at Case Western Reserve University School of Medicine in Cleveland, Ohio.

Regarding vSCCs' effect on women, Rao et al noted that vSCCs are the most common vulvar carcinomas, representing almost 90% of all vulvar carcinomas, and have an increased chance for significant morbidity and negative impact on quality of life due to the proximity of the tumors to the clitoris, urethra, vagina, anus, and inguinofemoral lymph nodes.

Currently, Mohs micrographic surgery (MMS) and advantageous intraoperative margin assessments are known treatments for early-stage vSCC. When treating early-stage tumors, gynecologists may use wide local excision, radical vulvectomy, lymph node dissection, and adjuvant chemoradiation for specific cases. For dermatologists, recognizing and understanding gynecologic-oncology recommendations helps to better understand when it is the right time to escalate treatment for their patients.

Methods

Rao et al performed a literature review to collect up-to-date treatment guidelines by searching for the terms "vulvar," "squamous cell carcinoma," "treatment," and "guidelines" together in PubMed and Google Scholar using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

> **"I'm glad there is increasing attention paid to women's health in dermatology because it is so important to our patients to continue building our repertoire of treatments through research, collaboration, and innovation."**
>
> Elizabeth Rao, fourth-year year medical student

Of the first 341 results, 18 articles remained after screening. From the 18 postscreened results, 13 articles related to the surgical treatment of early-stage vSCCs and were included.

According to Rao et al, vSCCs "are staged by the FIGO 2021 classification and the American Joint Committee on Cancer staging. Early-stage tumors are FIGO stage IA-IB or American Joint Committee on Cancer stage TI-TII, and under 4 cm in size, without suspicion of nodal involvement. Tumors larger than 4 cm in diameter or involving local structures such as the urethra are considered locally advanced and may follow a different treatment paradigm. FIGO stage IA tumors are under 2 cm in diameter, with less than 1 mm stromal involvement; stage IB are those greater than 2 cm or with greater than 1 mm depth."

The study authors noted that many guidelines recommend FIGO stage IA, unifocal tumors undergo local excision with minimum 8-mm margins on fixed tissue, while other societies recommend conservative 1- to 2-cm margins.

Guidelines from the German Society for Gynecology and Obstetrics and the German Cancer Society state that margins of 3 mm measured histologically may be acceptable. Adjuvant radiation therapy should be considered for diffuse disease, deep invasion (> 1 mm), or close margins (< 8 mm). For residual tumors, guidelines recommend reexcision or radiation therapy for unresectable tumors. For tumors invading deeper than 1 mm and extending greater than 2 cm, guidelines recommend escalation to radical vulvectomy or radical local excision, according to Rao et al's review.

Lastly, the collected guidelines determined that lymph node dissection via sentinel lymph node biopsy or inguinofemoral node dissection is recommended for FIGO stage IB and higher or depth of invasion greater than 1 mm. Lateral tumors (> 1 cm from midline) should undergo ipsilateral unilateral lymph node biopsy and midline lesions should undergo bilateral lymph node biopsy.

Moving Forward

"I hope that dermatologists recognize that they can and should help in the treatment of these malignancies. However, given the current guidelines, this may be a partnership with a gynecological oncologist. The current recommendations are very different than the treatment of similar tumors in other locations. We need further research into margin size and metastatic risk in vulvar SCC to better inform how we best utilize Mohs micrographic surgery to perform accurate, tissue-sparing surgery in this sensitive area, especially as treatments continue to advance," said Rao.

From their review, Rao et al encouraged dermatologists to be aware of the guidelines used by gynecologists/oncologists for the treatment of vSCC to better improve the quality of life of patients and to decrease the risk of morbidity. The authors also mentioned that there is limited data on the recurrence rates of vSCC after MMS and additional research may contribute to the evolving treatment guidelines.

"Guideline-based vSCC treatment includes faster escalation to radical vulvectomy and lymph node dissection than other high-risk sites treated by MMS such as facial mask areas. More narrow margins of [greater than] 3 mm on fixed tissue may be acceptable. Further research on margin size in vSCC may inform treatment focused on tissue conservation or intraoperative margin assessment, hallmarks of MMS," the authors wrote.

"Women's health care, particularly vulvovaginal disorders, is an area that could always use more research and more attention. Disorders of the vulvovaginal area can have large impacts on quality of life. I'm glad there is increasing attention paid to women's health in dermatology because it is so important to our patients to continue building our repertoire of treatments through research, collaboration, and innovation. Patients may see dermatologists or gynecologists first for these issues too, and so teamwork between specialties is crucial," concluded Rao.

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Replimune and Incyte to Collaborate on Clinical Trial for RP1 and INCB99280 for CSCC

Both companies are hoping to make a positive impact in the neoadjuvant setting of cutaneous squamous cell carcinoma.

Kaitlyn Bader, Senior Editor

Replimune Group and Incyte recently announced[1] their joint clinical trial collaboration and supply agreement to study Replimune's RP1 in combination with Incyte's INCB99280 for the treatment of cutaneous squamous cell carcinoma (CSCC). From their agreement, Incyte will initiate and sponsor the clinical trial of INCB99280 and RP1 in patients with high-risk, resectable CSCC, with the clinical trial expected to begin in early 2024. Replimune will supply Incyte with RP1 for the study and share equally in the costs of the study.

RP1 is Replimune's lead oncolytic immunotherapy product candidate and is based on a proprietary new strain of herpes simplex virus engineered for robust tumor selective replication and genetically armed with a fusogenic protein, GALV-GP R-, and GM-CSF, intended to maximize tumor killing potency, the immunogenicity of tumor cell death, and the activation of a systemic antitumor immune response.

Incyte's INCB99280 is a potent and selective small molecule oral PD-L1 inhibitor that has shown promising clinical activity and safety in patients with solid tumors, according to a news release. INCB99280 is also being evaluated in multiple phase 2 studies as monotherapy and in combination with other antitumor agents.

Replimune's proprietary RPx platform is based on a potent HSV-1 backbone with payloads added to maximize immunogenic cell death and the induction of a systemic antitumor immune response. The RPx platform has a unique dual local and systemic mechanism of action (MOA) consisting of direct selective virus-mediated killing of the tumor resulting in the release of tumor-derived antigens and altering of the tumor microenvironment to ignite a durable systemic response. According to Replimune, this MOA is expected to be synergistic with most established and experimental cancer treatment modalities, and with a proven safety profile the RPx platform has the versatility to be developed alone or combined with other therapies.

Regarding their work together, Robert Coffin, founder, president, and chief research and development officer of Replimune, said in the news release, "We are excited to enter into this collaboration with Incyte to explore the use of RP1 prior to surgery as we believe that our tumor-directed oncolytic immunotherapies could have a great impact in the neoadjuvant setting, both in cutaneous squamous cell carcinoma and in other cancer types, given the high rates of complete responses we've seen to date, and data indicating RP1 is generally very well tolerated."

"We look forward to collaborating with Replimune on this study evaluating INCB99280 and RP1 in patients with CSCC. Our oral PD-L1 program has shown promising safety and efficacy in early studies thus far, and we look forward to adding to the growing body of evidence for INCB99280 and learning more about its potential to improve clinical outcomes," Lance Leopold, MD, group vice president for clinical development hematology and oncology at Incyte, said in the release.

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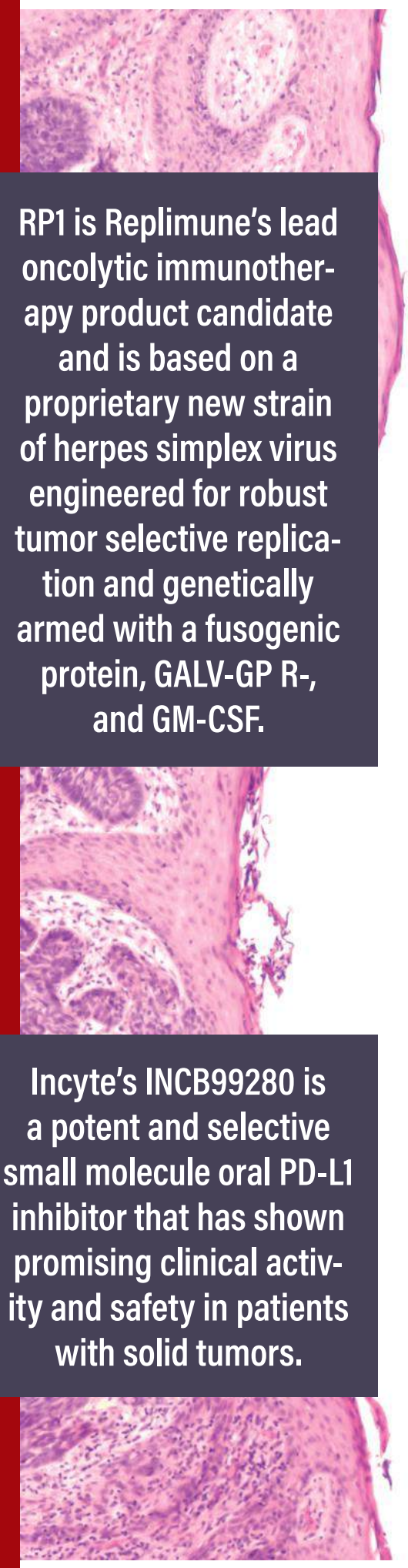

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Incyte's INCB99280 is a potent and selective small molecule oral PD-L1 inhibitor that has shown promising clinical activity and safety in patients with solid tumors.

Aircrews Face Increased Risk of Developing Skin Cancer

Beth Goldstein, MD, is a board-certified dermatologist and Mohs surgeon, the cofounder of Modern Ritual Health, and president and founder of Central Dermatology Center in Chapel Hill, North Carolina, as well as an adjunct clinical associate professor at the University of North Carolina at Chapel Hill.

Elianna Goldstein is cofounder and CEO of Modern Ritual Health in Chapel Hill, North Carolina.

Katherine McKay is a student in the Biomedical Sciences Master's Program at the University of Pittsburgh School of Medicine in Pennsylvania, as well as an intern at Modern Ritual Health.

ONE OF THE MORE CHALLENGING OCCUPATIONS regarding increased risk of skin cancer is aviation; aircrews are exposed to skin-damaging radiation and may face limited access to dermatological consultations. Each year, about 6.1 million adults are treated for basal cell and squamous cell carcinomas, making skin cancer one of the most common forms of cancer in the US. Sex, skin color, family history, immunosuppression, and age affect the risk of skin cancer; reducing exposure to radiation lowers the risk of developing skin cancer in the future. A critical risk factor is overall lifestyle and occupational exposure to the sun.

Exposure Risks

Frequent fliers, including pilots and cabin crew, are exposed to greater levels of UV and cosmic ionizing radiation (CIR) than the general population, leading to higher incidence of skin cancers. With an estimated 22.2 million flights worldwide, pilots are limited to 1000 h/y, supported by flight attendants up to 90 h/mo. Compared with the average 50 h/y for the average flier, aircrew are exposed to a significant amount of radiation.

UV radiation, measured on a scale from 1 to 11, is nonionizing radiation emitted by the sun. UV rays can penetrate the skin and damage DNA, increasing the risk of developing cancer. Although all aircrafts are equipped with windshields, protection from UV rays varies by aircraft, as do the materials and environmental conditions during flight, causing inconsistencies in exposure. For example, some windshields will block against UV-B rays, yet allow UV-A rays to penetrate. In other instances, increased altitude, snow, or cloud reflection during flight may increase overall UV radiation intensity. With every additional 900 m of altitude above sea level, there is a 15% increase in radiation intensity, translating to 2 times the intensity on the plane than on the ground. The reflective properties of snowfields and thick cloud covers reflect up to 85% of UV radiation. Aircrew flying for an hour at 30,000 ft receive the same amount of UV-A radiation as a 20-minute tanning bed session.

CIR is also known to cause cancer. Compared with UV, CIR is more harmful as it can cause atoms to lose electrons or break their nuclei. It can penetrate air, water, living systems, and thin materials. For the general population, small amounts reach the earth as the atmosphere and magnetic field shield against it. With higher altitudes and more polar latitudes, this protection decreases, and exposure risks increase.[1] A meta-analysis conducted by Sanlorenzo et al[2] reported that based on higher levels of cosmic and UV radiation exposure, pilots and airline crew are at approximately 2 times the incidence of melanoma as the general population. Although aircrew are exposed to higher levels of radiation, both UV and CIR, they are not classified as radiation workers in the US. Aircrew specifically are exposed to CIR at higher levels, ranging from 0.2 to 5 mSv/y. To put this in perspective, 0.1 mSv of CIR is comparable to 1 chest x-ray.[3]

Education and Prevention

The general population flying on average 50 h/y should be aware of their exposure to increased radiation at elevation, but their daily life habits most likely have more of an impact. In educating cabin crew on the risks, knowing the patient's specific employment exposure is vital.

Flight attendants get exposed to slightly more radiation than flight captains, as captains' windshields are sometimes better at shielding radiation than passenger windows. Flight routes also alter the exposure intensity, as crews flying at lower altitudes or closer to the equator experience 2 to 3 times less CIR exposure as those flying at higher altitudes and closer to the poles. As with UV, CIR is also affected by elevation. Day or night, ionizing radiation is present when flying above 20,000 feet; therefore, exposure is measured in hours spent at altitude rather than time of day.

Combined UV and CIR exposure puts aircrew at a significantly higher risk for skin cancers than the general population. Airlines should educate their employees on the occupational risks, emphasize full-body self-examinations, and provide affordable access to dermatology and oncology practices. The best way to prevent serious complications from skin cancer is early detection. Aircrew lifestyle puts them at a disadvantage for consistent check-ups, but scheduling time with a primary care provider (PCP) that utilizes companies like Modern Ritual Health, which evaluate suspicious lesions through dermoscopy, is essential in early detection and care navigation. Checking for changes in the appearance of a mole or spots, nonhealing lesions, scaly patches, and changes in fingernails or toenails are all signs of skin cancer that warrant a checkup.

Dermatologists with aircrew as patients should emphasize wearing broad-spectrum sunscreens with a sun protection factor (SPF) of 30+, reapplying every 2 hours, and consider covering skin if uniforms allow. Opting for shorter flights at lower altitude and close to the equator will also reduce exposure. Providing patients with education and affordable access to dermatology care is key in preventing skin cancers. Credible dermatology providers are also utilizing social media to share information on platforms like TikTok and Instagram.

Although not often thought of as an occupational health hazard, aircrews face increased incidence of skin cancers due to radiation exposure. Aircrews, airlines, and dermatologists can take proactive steps, but awareness and access are necessary. UV and CIR in aviation result in skin cancers through slow accumulation, similar to how many sunburns at a young age will have lasting damage over 50 years. Dermatologists and airlines should educate aircrew on minimizing exposure, such as using a tinted broad-spectrum SPF 30+; reapplying every 2 hours to areas not covered by clothing; and opting for shorter, lower-altitude flights. The exposure aircrews experience is incremental and may not manifest for years. Occupations that require frequent travel may make it more challenging to schedule consistent checkups with a dermatology provider. New and emerging technologies such as mole mapping at home, virtual appointments, or other offerings may help expand access to early detection and screenings.

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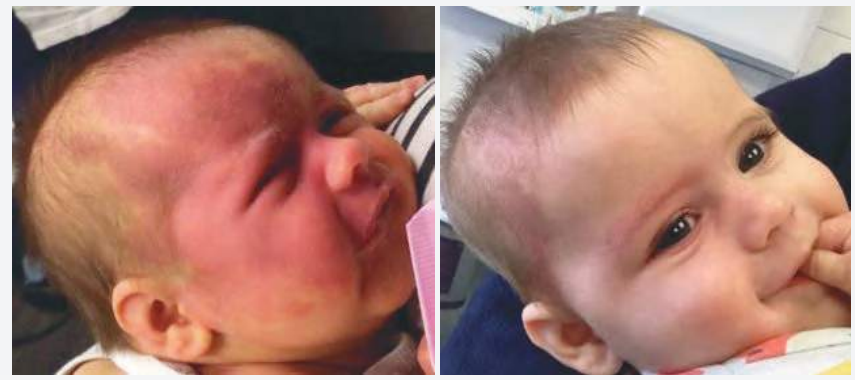

Before treatment at 3 weeks of age | After Vbeam treatments at 4 months of age

Courtesy of Roy G. Geronemus, MD., Laser & Skin Surgery Center of New York
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Expert Insights on Rapid Weight Loss, Semaglutide, and Aesthetic Procedures

Isabella Tan, Correspondent

Advances in medical treatments, such as semaglutide (Ozempic; Wegovy), have opened new avenues for shedding unwanted pounds quickly. The rapid weight loss and impact on skin has coined the term "Ozempic face" on social media and some online news platforms.[1] While a patient's journey toward weight loss for overall better health can be exciting for them, it involves multifaceted considerations that extend beyond the numbers on a scale when it comes to sagging or excess skin and the psychosocial role it plays. Expert dermatologists and aesthetic physicians shed light on the comprehensive approach required to navigate the complex intersection of rapid weight loss, aesthetic procedures, and promoting self-confidence among patients.

Transparent Communication and A Multidimensional Approach

Glynis Ablon, MD, an associate clinical professor of dermatology at the University of California, Los Angeles, and owner of the Ablon Skin Institute and Research Center in Manhattan Beach, California, underscores the paramount importance of transparent communication between patients and their health care providers. "I think it's critical for an aesthetic physician to discuss all concerns and medications with their patients. I have individuals who are thinking of starting weight loss medication and those who are currently [on it]. It's important to explain that any quick weight loss activity can lead to more dramatic changes in skin laxity and deflation. To address these concerns, physicians must take a 3 dimensional approach addressing structure, morphology and symmetry in order to successfully and naturally 'reinflate' these patients or perhaps even better," she said.

Ablon also elucidates a noteworthy phenomenon: quick weight loss can induce substantial changes in skin laxity and deflation. This comprehensive strategy facilitates the natural "reinflation" of the skin, thereby fostering an authentic and harmonious aesthetic outcome. The integration of aesthetics with medicine is crucial to ensure that the physical transformation resonates with an individual's self-image.

Revitalizing Facial Structure: Meticulous Techniques for Harmonious Outcomes

Suneel Chilukuri, MD, founder and director of Refresh Dermatology in Houston, Texas, expounds upon the insights gained from treating patients undergoing weight loss interventions. "We have observed shifts in facial structure among many of our patients on these therapies, particularly noting significant depletion in lateral temporal, and middle fat pads," he said. To rectify these structural changes, Chilukuri employs a meticulous layering technique, effectively reintroducing volume and structure. Furthermore, he employs biostimulation to harness the body's innate collagen production, thereby mitigating the cosmetic effects of rapid weight loss.

Striking a Balance: The Synergy Between Ozempic and Aesthetic Procedures

Doris Day, MD, clinical associate professor of dermatology at the New York University Langone Medical Center in New York, New York, shared invaluable insights into the symbiotic relationship between semaglutide, steady weight loss, patient strength training routines, and cosmetic procedures. Day's approach is rooted in balance, encouraging patients to embrace a consistent, feasible exercise routine to maintain muscle mass while undergoing semaglutide-associated weight loss of 1-2 pounds a week. Central to her methodology is the art of anticipation; as patients progress, Day adeptly adjusts procedures to accommodate evolving anatomical changes. "It's important to collaborate with patients, align cosmetic goals with Ozempic's effects, and ensure satisfying results," she shared.

Skin Health: A Crucial Component of Holistic Transformation

Leslie Baumann, MD, owner of Skin Type Solutions in Miami, Florida, champions the significance of skin care in the context of rapid weight loss. Her conviction in the potential of retinoids and vitamin C to prevent sagging is a testament to her deep understanding of skin health. Notably, Baumann takes her dedication a step further by tailoring skincare regimens through her pioneering 16 skin type system. This personalized approach allows her to curate the ideal regimen for each individual, capitalizing on the efficacy of specific ingredients.

Baumann's observations underscore a fascinating link between semaglutide usage and improved skin health. Lower blood sugar levels resulting from semaglutide's impact on weight loss may contribute to enhanced skin vitality.[2,3] This revelation positions semaglutide as not only a catalyst for weight loss but also a valuable asset for skin health maintenance. Baumann's insights illuminate the interconnectedness of the body's transformations, with the skin adjusting gradually to the evolving physique.

Discovering Your Patient's Unique Skin Needs

Take a look at important questions Baumann asks her patients to best identify their skin history and future regimens.

Strategies to Restore Facial Harmony Through Fillers

"I have many patients with rapid significant weight loss, from either Ozempic, gastric bypass, diet and exercise, or even illnesses like COVID," said Robyn Siperstein, MD, owner of Siperstein Dermatology Group in Boynton Beach, Florida. Sheunveiled her strategy to restore facial balance in those grappling with

>> **Expert Insights** *continues on* **28**

Periorbital Rejuvenation: Comprehensive Assessment and Product Choice Are Key to Results

With a wide range of aesthetic options available, clinicians can create a personalized approach to addressing age-related changes around the eye to give patients the natural-looking results they desire.

Joely Kaufman, MD, Correspondent

Aging happens at every layer in the skin and also its underlying structures, including subcutaneous fat, muscle, and bone. The area around the eyes is among the first to show signs of aging. Ultimately, the focus is on rejuvenation and brightening of the skin in that area, opening the eye and lifting the eyelid and eyebrow.

Multiple changes can occur in the periorbital area, starting with fine lines around the eyes, which appear as a result of muscular contraction (smiling and squinting). The development of wrinkles in this area is also dependent on the way someone animates. Patients with fairer, thinner skin will show those lines earlier.

Another top concern for patients is undereye "bags." Here, the fat pads can herniate from beneath the muscle, leading to puffiness that patients commonly refer to as bags. Other concerns for our cosmetic patients are hollowing under the eye and periorbital hyperpigmentation. It is important to distinguish between all 3 of these to provide appropriate treatments.

Comprehensive Consultation

When it comes to the periorbital area, it is vital for patients to have a thorough consultation with a dermatology specialist who understands the various aspects of periorbital aging. On social media, content around undereye filler is ubiquitous, leading individuals to think it works for everyone. The best candidates for these products are those with undereye hollowing, good skin quality, and a limited amount of fat herniation. Hyaluronic acid (HA) gel (Volbella XC; Allergan) received FDA clearance for this indication in 2022. This year, another HA filler, Restylane EYELIGHT (Galderma), also received clearance for the improvement of infraorbital hollows. Other rejuvenating products are undergoing additional clinical studies in the infraorbital area, including RHA Redensity (Artemedica).

When evaluating the periocular area, I first assess the skin. If the skin is the main problem, perhaps discoloration, for example, we may start patients on topical products. I tell patients that it is important to invest in high-quality eye creams or serums, as the skin in this area can be sensitive. My personal favorites are EyeMax (skinbetter), Alastin eye cream (Galderma), and Revox Line Relaxer (Revision Skincare).

When we start seeing fine lines or crow's feet around the eyes, we may begin with neuromodulators such as onabotulinumtoxinA (Botox; Allergan Aesthetics), daxibotulinumtoxinA-lanm (Daxxify; Revance Aesthetics), or abobotulinumtoxinA (Dysport; Galderma). To address crepiness around the eye and laxity in the lower lids in patients not ready for surgery, we can use microneedling alone or pair it with platelet-rich plasma (PRP). Fraxel nonablative (Solta Medical) or carbon dioxide lasers are good choices for under the eye for patients not wanting surgery. Devices aimed at lifting the brow, including Ulthera, are also a safe option for this area.

Next, we consider ways in which we can change or open the eye's aperture. A neuromodulator can provide a small amount of medial and lateral brow lift when injected in the appropriate manner, but until recently, options for lifting the eyelid proper were mostly surgical. Oxymetazoline hydrochloride ophthalmic solution 0.1% (Upneeq; RVL Pharmaceuticals, Inc) is the first FDA-approved pharmaceutical treatment indicated for acquired blepharoptosis in adults.[1] The topical application of the drug stimulates the α-adrenergic receptors on the Müller muscle, resulting in temporary contraction and eyelid

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Common Pitfalls

There are 2 common mistakes made when it comes to periocular rejuvenation. First, when too much neuromodulator is applied in the forehead of an older patient who already has a low-lying brow and low-lying lids, this will drop the brow and lid and the eye area will look more aged. So, although the patient may have no lines at all in the forehead, they do not look younger or more rested because their eyelids now appear heavy.

The second mistake has to do with the use of undereye filler and the misconceptions patients have from social media. Infraorbital filler is a great treatment for those patients with undereye hollowing; however, for those with very thin skin, or those with just hyperpigmentation or bags, it might not be the best choice. For those who already have significant undereye swelling or fat herniation, undereye filler can make that area look worse due to the hydrophilic nature of hyaluronic acid.

It is important for practitioners and patients to understand that not every person is a candidate for every type of treatment, whether it is microneedling with PRP, undereye laser, fillers, a neuromodulator, or a combination of options. Ultimately, some patients will be candidates for surgery; many oculoplastic interventions can be done under local anesthesia. Even invasive procedures are more accessible than ever before.

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gauntness. Siperstein emphasizes global volumization with fillers to mimic lost fat pads, using a layered approach for smoother contours. Advanced techniques like temple hollowness correction and cautious use of stimulatory fillers are often involved in her approach. In navigating the challenges of sagging skin and thinner facial layers, Siperstein employs a meticulous and gradual strategy to ensure optimal outcomes, while promoting harmonious transformations for patients on their journey to self-confidence.

Conclusion

In the pursuit of rapid weight loss and aesthetic enhancements, individuals often face a myriad of concerns and choices. The wisdom of experts including Ablon, Chilukuri, Day, Baumann, and Siperstein shines a light on the importance of addressing these matters holistically, encompassing both the physiological and psychological dimensions of self-confidence. As the medical landscape continues to evolve, the integration of semaglutide and aesthetic procedures holds immense promise. Through open communication, multidimensional assessments, and a commitment to holistic harmony, patients can navigate their journeys with the support of skilled physicians, ultimately achieving self-assurance and well-being.

Isabella Tan is from Potomac, Maryland, and is a rising medical student at Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey.

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>> **Periorbital Rejuvenation**
continued from **27**

elevation. Approved for everyday use, it starts working within 20 minutes; 1 drop lasts for about 6 to 8 hours.

The results from Upneeq are noticeable yet natural; patients do not end up looking "bug eyed" or scared. It is packaged in individually wrapped, single-use droppers so it is easy to travel with and there is no worry about contamination of an eye dropper. I use mine to ensure I look bright-eyed, well rested, and youthful for special events. It provides a nice boost to open the eye for adults of any age who are experiencing lid lowering. Upneeq has almost no downside and is complementary to our other offerings. I have prescribed it for a wide range of patients who are very satisfied with the results. I have found it to be a wonderful addition to our full slate of offerings.

Although all these noninvasive and minimally invasive procedures help provide periorbital rejuvenation, once a patient has a significant amount of eyelid hooding and laxity, I send them to my oculoplastic colleagues for a surgical evaluation.

Conclusion

Many factors contribute to aging of the eye area, and all patients should be evaluated for exactly what their concern is to determine the appropriate treatment. With so many different options on the market, it is an exciting time to be in aesthetics and dermatology.

Joely Kaufman, MD, is a board-certified dermatologist, fellow of the American Academy of Dermatology, and the director of Skin Associates of South Florida in Coral Gables. She is a voluntary clinical associate professor at the University of Miami Department of Dermatology and Cutaneous Surgery in Florida, where she teaches residents and fellows injection and laser techniques. She is extensively involved in clinical research at the Skin Research Institute in Coral Gables, Florida and is a principal investigator on several clinical trials in dermatology, including pivotal FDA studies on neuromodulators, fillers, and devices for the aesthetic market.

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cosmetic conundrums with Zoe Diana Draelos, MD

Understanding the Role of Amino Acids and Proteins in Skin Care

USING AMINO ACIDS, PEPTIDES, AND PROTEINS in skin care products is not new. One of the earliest humectant moisturizer ingredients that functioned like a sponge to hold water on the skin surface was hydrolyzed collagen. The collagen was obtained by cooking cowhides and retrieving the collagen fragment–rich broth for addition to moisturizers. Collagen is made up of around 4000 amino acids, but the fragments created by heating cowskin are erratic, unpredictable, and undefined. New synthetic chemistry allowed the creation of peptide fragments one link at a time from specific amino acids that could be biologically active through receptor-mediated activity. This manufacturing method is tedious and expensive but highly reproducible, allowing the creation of well-defined peptides. Recently, the cost of peptides has dropped, allowing this ingredient to leave the prestige cosmetic market and enter the mass cosmetic market, which is why there are now a plethora of skin care products utilizing this technology.

The Mechanism of Peptides

Peptides work on the lock-and-key model of receptor-mediated activity. The peptide is a fragment of a larger molecule, such as type I collagen, which is presented to the cell membrane and recognized by a specific receptor molecule. This in turn initiates some type of biologic response through a conformational change in the transmembrane structure, leading to a cascading of events in the cell's interior biochemistry. This cascade leads to amplification of the signal sent by the peptide, which is used in cosmetic formulations in parts per million based on cost.

Peptides need to reach the viable layers of the skin to work. The skin is very adept at keeping out proteins, which are the basis for most allergenic substances, such as peanuts and shellfish. Depending on the size of the peptide, penetration may also be limited. The penetration of short peptides is enhanced through palmitoylation, which involves the addition of a free fatty acid, such as palmitic acid, to the peptide.

Types of Peptides Available

There are 3 families of peptides: signal peptides, carrier peptides, and neurotransmitter-inhibiting peptides. Signal peptides are intended to act as messengers triggering the synthesis of collagen by fibroblasts. Many of these data come from wound healing studies. Carrier peptides are used to deliver ingredients into the skin, but only the peptide delivering copper has been commercialized. Neurotransmitter-inhibiting peptides are thought to inhibit acetylcholine release at the neuromuscular junction.

Most Common in the Marketplace

The most widely used peptides are the signal peptides, which form the basis for antiaging claims in many moisturizer formulations.

Neurotransmitter Peptides

The neurotransmitter peptides were developed to mimic the effect of neurotoxins. The most popular neurotransmitter peptide is acetyl-glutamyl-glutamyl-methoxil-glytaminyl-arginyl-arginylamide (Argireline), which is said to interfere with the release of acetylcholine by destabilizing the protein complex. Pentapeptide-3 is another amino acid sequence, but the sequence is unknown. This peptide is said to act like curare at the postsynaptic membrane. Achieving neurotoxin effects with topical agents is challenging as the peptide must deeply penetrate the skin, reach the receptor, and remain in place long enough to produce a physiologic effect.

Zoe Diana Draelos, MD, is a consulting professor of dermatology at Duke University School of Medicine in Durham, North Carolina, and editor in chief of *Dermatology Times*. ■

There are several commercialized peptides:

1. **Valine-glycine-valine-alanine-proline-glycine (VGVAPG)**
This hexapeptide is thought to stimulate the production of collagen and elastin. It attaches itself to the fibroblast membrane but must be penetration enhanced with palmitic acid. It is found in many cosmeceutical preparations listed as palmitoyl oligopeptide.

2. **Lysine-threonine-threonine-lysine-serine (KTTKS)**
This is the most widely used peptide in cosmeceuticals and is a fragment of procollagen type I. It has a positive feedback effect on the synthesis of collagen types I and II. It too must be penetration enhanced with palmitic acid. However, bigger peptides are more expensive, so there has been a trend to reduce the number of amino acids and make simpler signal peptides.

3. **Lysine-valine-lysine (KVK)**
This tripeptide has been shown to decrease collagenase levels and increase collagen levels in vitro. It too is combined with palmitic acid and appears in cosmeceuticals as palmitoyl tripeptide-3/5.

4. **Lysine-phenylalanine-lysine (KFK)**
This tripeptide is sold linked to elaidic acid. It is thought to activate transforming growth factor beta and inhibit collagenase, thereby increasing collagen levels.

pigmentary disorders

Addressing Cultural Disconnect in Patients With Vitiligo

Clinicians can use culturally competent care to ease patients' concerns with identity and better understand the emotional toll of the condition.

Emma Andrus, Assistant Editor

Among the myriad of challenges faced by patients with the condition is a struggle with personal identity and a sense of disconnect from their own culture as they reconcile with their visibly changing skin.[1,2]

Omar Noor, MD, FAAD, a board-certified dermatologist who practices in New York and New Jersey, says providing culturally competent care is the key to helping patients who are struggling with their identity.

"Culturally competent care is something that you have to think about when you're treating patients," Noor said. He explained various cultures may have specific stigmas or sensitivities, especially with vitiligo, and it is important to be aware of this. "Sometimes you have to make it a point to truly put yourself in the patient's skin and appreciate where they're coming from," he said.

Noor provides dermatology clinicians with pearls and best practices for culturally competent and compassionate care in the management of vitiligo.

Recognize the Effects of the Patient's Changing Appearance

Although loss of pigment may be more apparent in patients with darker skin types due to a greater contrast, Noor said it is important to recognize that this does not diminish the effect of pigment loss on white patients.

"As we see that in our darker skin types, we have to appreciate its effects not only on the patient, but [in] the way the patient views themselves in the eyes of their friends, their family, the people around them," he said.

"Sometimes you have to make it a point to truly put yourself in the patient's skin and appreciate where they're coming from." —Omar Noor, MD, FAAD

Practice Compassion and Encourage Appreciation

In addition to the stigma[3] surrounding vitiligo, patients with ties to certain cultures may face myths and misconceptions centered around their condition. According to a 2022 abstract published in *Dermatological Reviews*, there are several prevalent myths and misconceptions about vitiligo in vaious regions of the world, including the Middle East and Southeast Asia, including confusing vitiligo with leprosy.[2]

Noor shared that a patient with vitiligo depigmentation located on the arm once asked whether the arm could be amputated, all because of the stigma.

"That is the impact that vitiligo can have, psychologically, on another human being," Noor said. "For a lot of these patients, some people even think that it might even be contagious. You have to be very compassionate, and you have to be

educational. You want these patients to understand that this is not their fault and that we are learning more about this autoimmune condition that we call vitiligo, and really educating them on why it's happening and the different tools that we have in order to improve that."

Offer the Appropriate Mental Health Resources to Your Patients

"The most important thing is to start by educating an individual that's looking to such an extreme. They may have a different mindset: 'I have this hidden disease. Maybe it's contagious. I can't hold my children; I'm going to give it to them by touching them.' Educating around what they have, and how we have tools to help repigment the skin. Once they can appreciate that, they can appreciate that it's going to take time, but we're going to move in a positive direction," Noor said.

Due to the psychological effects of vitiligo,[1] Noor believes ensuring patient access to appropriate mental health care and resources is important. "Whether it's a psychiatrist or primary care doctor, making sure that they have the appropriate network around them so that not only do they understand, but their family understands, their friends understand, what they're dealing with, what they're treating, and then we can all work together towards a resolution," he said.

Be Mindful When Balancing Appreciation and Offering Treatment Perspectives

"Vitiligo is especially challenging, mostly because we only recently have our first FDA-approved option for treatment,[4] and our treatment options have been limited previously," Noor said.

"But the other major, challenging component for vitiligo is the fact that we have patients in dermatology, in skin diseases, whether it's acne, psoriasis, atopic dermatitis, everything that we talk about and we do: 'I want to get you better, and I want to get you better faster.' With vitiligo, that is not the case. It's just not the way the disease works. We have to be patient, and we have to make sure that our patients are patient because the repigmentation takes time. They have to be aware that it's going to take effort. It's going to take time, but we'll get there together."

Encourage Continued Patient Education to Eliminate Vitiligo Stigma

According to Noor, patient education is the foremost best practice for eliminating vitiligo stigma and providing more compassionate care. "We know that vitiligo is an autoimmune condition. We know that genetics plays a very large role in that, but at its core, vitiligo is an inflammatory condition. Understanding that we can now attack vitiligo with topical JAK inhibition really allows us to address that in our patient," Noor said.

"Educating around the treatment: It's going to take time; some areas may read pigment faster than other areas. We're lucky that areas like the face that have more hair follicles will repigment faster. Areas that have less hair follicles will repigment slower, but we have to have that conversation with the patient so that they can know what to expect going forward. And as we become more educated as providers, then we can then go on to educate our patients more," concluded Noor.

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atopic dermatitis

Precision Prescribing With a Topical Medication Volume Calculator

Lauren Buchanan, MA, Managing Editor

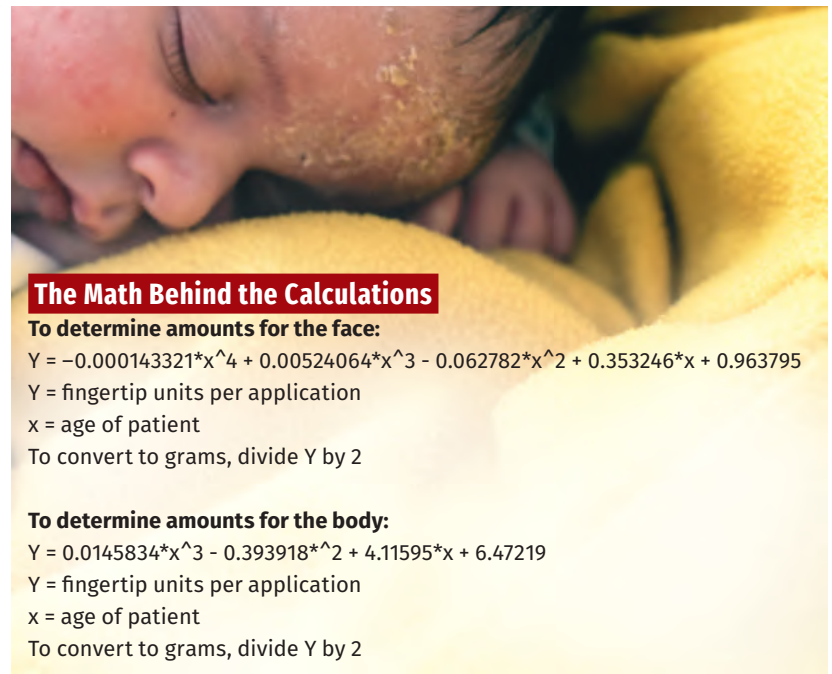
A pediatrician's role in the treatment of atopic dermatitis (AD) is important yet faces barriers to success. Lawrence Eichenfield, MD, vice chair of the dermatology department at UC San Diego (UCSD) School of Medicine and chief of pediatric and adolescent dermatology at Rady Children's Hospital-San Diego, both in California, acknowledged that pediatricians often refer patients with mild AD cases to dermatologists. He and his colleagues at Rady/UCSD wanted to provide a solution to help with vetting serious cases to dermatologists. The topical medication volume calculator (TMVC) was presented during the session "Research Updates in Pediatric Dermatology" at the Society for Pediatric Dermatology 48th Annual Meeting in Asheville, North Carolina, from July 13 to 16.[1]

Eichenfield cited reasons pediatricians often send mild AD cases to dermatologists, including limited knowledge about the condition and management options, steroid phobia, and insufficient quantity of topical medications prescribed. Topical agents are not prescribed in defined quantities as oral medications are.

The solution to help overcome these barriers was the development of an electronic medical record (EMR) ordering tool for streamlined AD topical prescriptions. A similar tool was developed for pediatric acne care. The goals in developing the EMR-based tool were to increase self-reported confidence with AD management by pediatricians, improve performance on knowledge-based examinations, and increase proportion of AD-coded visits associated with the prescription of the appropriate therapy.

Software Development

"The TMVC is a logarithmic algorithm designed to compute volume of topical medication," Eichenfield explained. "It utilizes a cubic regression model, based on grams of topical ointment or cream needed to cover 100% of the body." The calculator was built into the standard EMR (Epic) and relies on 2 data points: patient age and estimate of body surface area involved, excluding the head. Dosing is generated weekly and allows the estimation of quantity to be used over a month.



The Math Behind the Calculations

To determine amounts for the face:

Y = −0.000143321*x^4 + 0.00524064*x^3 - 0.062782*x^2 + 0.353246*x + 0.963795

Y = fingertip units per application

x = age of patient

To convert to grams, divide Y by 2

To determine amounts for the body:

Y = 0.0145834*x^3 - 0.393918*^2 + 4.11595*x + 6.47219

Y = fingertip units per application

x = age of patient

To convert to grams, divide Y by 2

A pathway was developed, allowing clinicians to easily prescribe standardized medication with standardized precision, which is integrated with the TMVC to generate volumetric prescriptions for topical steroids and nonsteroidal agents. Patient instructions are automatically generated from the TMVC data entered and provide week-by-week instructions for their new prescription.

Launching the Tool

TMVC developers created a standardized educational module to present to pediatric practitioners. Reinforcement activities included a podcast and tutorial video to ensure the calculator was utilized to its fullest potential.

Results

Eichenfield reported pre- and postintervention surveys from clinicians utilizing the calculator noted improvements in comfort level with AD, understanding of pathophysiology and epidemiology, and prescribing topical and systemic therapies for AD. EMR data also showed an increased number of topical prescriptions among a similar number of AD visits, including topical corticosteroids.

This project was implemented at the start of the COVID-19 pandemic, which delayed the utilization and training for clinicians using the TMVC. Investigators and developers also learned that the utilization of automatic prescription writing is more limited than desired in the field. "There is a lot of future work to develop the tool and evaluate the utility of the TMVC on medication adherence and treatment outcomes that would be useful," Eichenfield concluded.

Craig Burkhart, MD, MPH, owner of Burkhart Pediatric & Adolescent Dermatology in Cary, North Carolina, served as a course director for this year's Society for Pediatric Dermatology Meeting and was captivated by Eichenfield's presentation. "Dr. Eichenfield hit on an important concern for prescribers and families—how much topical steroid is appropriate to prescribe and use," he said. "A large part of eczema counseling is educating on appropriate use of topical steroids so that children's skin improves, while at the same time avoiding side effects from overapplication. I can see the tool being useful by giving families and prescribers a clear quantity that is likely to strike the right balance between safety and efficacy. The tool is also useful in that it has a holistic approach of additionally supporting families with automatically sending week-by-week instructions and providing standardized educational modules for prescribers. The tool sounds empowering for patients and prescribers and looks like a useful educational aid for dermatologists who care for eczema patients."

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Analyzing the Safety of JAK Inhibitors in Atopic Dermatitis Treatment

Lauren Buchanan, MA, Managing Editor

"I think it's important to remember that until relatively recently, the main systemic therapies we had for atopic dermatitis [AD] were traditional immunosuppressive therapies, as well as systemic steroids," said Ruth Ann Vleugels, MD, MPH, MBA, vice chair of academic affairs in the department of dermatology at Brigham and Women's Hospital in Boston, Massachusetts. She and Christopher Bunick, MD, PhD, associate professor of dermatology at Yale University in Middlebury, Connecticut, did a deep dive into multiple studies about Janus kinase (JAK) inhibitors in AD treatment during the *Dermatology Times Between the Lines* custom video series, "Expert Insights on the Use of Oral JAK Inhibitors for Atopic Dermatitis: Raising the Bar for Standard of Care."

Risk Factors in Prescribing JAK Inhibitors

Vleugels has relied on safety data to develop her comfort level in prescribing JAK inhibitors compared with the traditional treatments including steroids, cyclosporine, and methotrexate. "A really important point is that some of the concerns with JAK inhibitors came from the data from patients with rheumatoid arthritis [RA], who have an increased risk of clotting, cardiovascular risk factors, and malignancy at baseline," she explained. "This makes the study population different from the population we're talking about in dermatology, like our patients with AD."

She and Bunick looked at a study focusing on upadacitinib-treated patients with RA.[1] "The clotting and cardiovascular risk factors are not higher than when those same patients with RA are treated with methotrexate or adalimumab or even RA at baseline," Vleugels said. "Similarly, when they follow those patients over time, there's no increased risk. That's crucial in thinking about how we consider using medications. We have to know the patient population well."

Vleugels is adamant about considering these risk factors for patients when prescribing JAK inhibitors and that patient selection is important. She shared, "I'd strongly prefer to avoid systemic steroids in repeated courses for any of my patients with AD. They're not a long-term solution. Some of these problems we're discussing in terms of clotting risk and cardiovascular outcomes are higher in patients on systemic steroids or cyclosporine than the medications we're talking about today, which are also more efficacious. That's an important point to think about when you're counseling patients."

JAKs Versus Immunosuppressive Therapies

Bunick published another study with a former student now in residency comparing JAK inhibitors to traditional systemic immunosuppressive therapies—specifically steroids, methotrexate, and cyclosporine, which were the most advanced treatment options a decade ago.[2]

"What we're going to see is that in this data there was not a lot of AD-specific data for us to draw numbers from. We had to draw from what was out there to do our initial comparisons," Bunick said. "In the design, we look at upadacitinib [Rinvoq; AbbVie] and abrocitinib [Cibinqo; Pfizer], both doses of the medicine for collecting adverse event incident rates, and we did a literature search looking for incident rates of adverse events between the oral JAKs and the traditional systemic immunosuppressive therapies, focusing on malignancy, nonmelanoma skin cancer, major adverse cardiovascular events, [and] venous thromboembolism."

He reiterated that the major limitation of the study was that many events were not documented in AD patients. He explained, "I don't think that we had a reason to understand them prior to a few years ago when the JAK inhibitors were starting to be in the clinical trials. But clearly, the next step is to understand these events in AD patients, so we can do a comparison of the traditional systemic immunosuppressives vs JAKs in AD patients only. But for now, this is the best comparison that we have."

Bunick and his student observed that on average, the event rates from methotrexate cyclosporine and systemic corticosteroids were higher than the JAK inhibitors for adverse events or special interests. "And how does this help us clinically?" he asked. "Well, if you're trying to develop a treatment pyramid, it suggests that the JAK inhibitors should be considered ahead of these traditional immunosuppressive drugs for AD patients, and with respect to systemic corticosteroids, systemic corticosteroids were the highest. They had the highest event rates per 100 patient-years of any of these medicines."

Strategically Rethinking Systemic Steroids

Bunick and Vleugels tend to avoid systemic steroids when they develop AD treatment plans for patients because they believe it isn't a long-term, effective option. "I really don't want to use them because they have so many comorbidities and I really want to reach for agents that give me longer term more effective control. I'm really trying to use systemic steroids extremely rarely, and these days I don't have to use them almost ever. Obviously, in the past, I wasn't that fortunate. But currently, there's not often very many instances where I would really need to reach for systemic steroids in a patient with AD," Vleugels shared.

Bunick echoed, "I do not use systemic corticosteroids ever for my eczema patients, even when patients ask for them...JAK inhibitors have a very rapid onset of action because of where they work inside the cell. Yet, we also just saw safety data and as well as efficacy data from the network meta-analysis showing that the JAK inhibitors are also safe and effective over the long term."

Many of Vleugel's patients have been on JAK inhibitors anywhere from 5 to 8 years. "I think this is really important to think about the fact that I would prefer to have a patient on a JAK inhibitor for that duration or longer, very easily and much more readily than I would prefer for them to be on systemic steroids, and there's no question about that in my mind for my patient population," she concluded.

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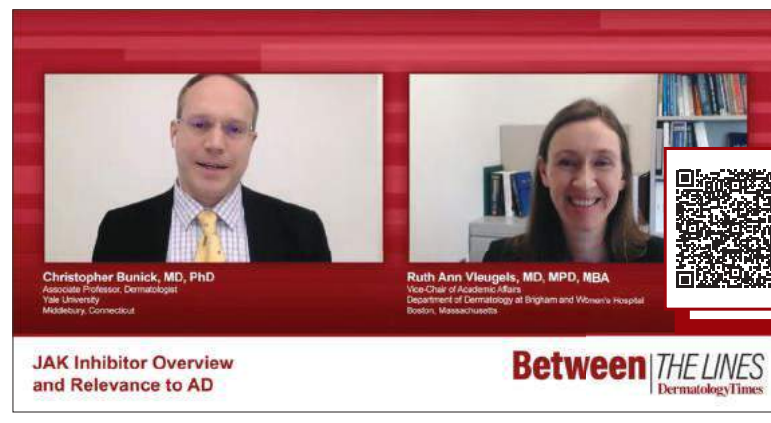

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INDICATION[1]

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.

IMPORTANT SAFETY INFORMATION[1]

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 TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

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

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of 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.

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.[1]

FOR UNCONTROLLED AD PATIENTS

DISRUPT EXPECTATIONS

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~4 years of safety data in AD[3]

RAPID RELIEF

- EASI 75 results as early as Week 2 and reduction of worst pruritus NRS ≥4 measured at Week 16 with results observed at 2 days after first dose[1,4]
- No to little itch (NRS 0/1) rates measured at Week 16[5,6]

DURABLE CONTROL

- Co-primary endpoints EASI 75 and vIGA 0/1 controlled at Week 16[1]
- Response rates for skin & itch observed up to 52 weeks[5]

ROBUST RESPONSE

- 90% skin improvement (EASI 90) measured at Week 16[1]

LEARN MORE AT RINVOQHCP.COM/AD

In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, 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 that 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.

Please see additional Important Safety Information on the following pages of this advertisement.

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

IMPORTANT SAFETY INFORMATION[1] (cont'd)

RINVOQ® upadacitinib

ONE PILL, ONCE-DAILY

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

GASTROINTESTINAL PERFORATIONS
Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES
Neutropenia
Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia
Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

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

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

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

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

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

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

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

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

Dosage Forms and Strengths: RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

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

EASI 75=improvement of at least 75% in lesion extent and severity. EASI 90=improvement of at least 90% in lesion extent and severity. vIGA 0/1=clear or almost clear with at least 2 grades of reduction from baseline. Worst pruritus NRS ≥4=improvement (reduction) in worst pruritus NRS ≥4 points from baseline.

*As of 7/2022. Source: Integrated Symphony Health (PatientSource) and IQVIA (NSP).

AD=atopic dermatitis; EASI=Eczema Area and Severity Index; NRS=numerical rating score; vIGA=Validated Investigator Global Assessment.

References: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc.; 2022. **2.** DOF [Data on File]. ABVRRTI74605. **3.** DOF [Data on File]. ABVRRTI74922. **4.** Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. 2021;397(10290):2151-2168. **5.** Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the Measure Up 1 and Measure Up 2 randomized clinical trials. *JAMA Dermatol*. 2022;158(4):404-413. **6.** Reich K, Silverberg JI, de Bruin-Weller MS, et al. Deep and rapid response on skin clearance and patient-reported outcome measures with upadacitinib with or without topical corticosteroids in moderate to severe atopic dermatitis: results from three phase 3 studies (Measure Up 1, Measure Up 2, and AD Up). Poster presented at EADV 2021.

abbvie

RINVOQ® (RIN-VOKE) (upadacitinib) extended-release tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

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

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Adverse Reactions]*. 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, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with RINVOQ 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 RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

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

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 RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Atopic Dermatitis

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.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.

Ankylosing Spondylitis

RINVOQ is indicated for the treatment of adults with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Non-radiographic Axial Spondyloarthritis

RINVOQ is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

CONTRAINDICATIONS

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- 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 RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ. RINVOQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

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

Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

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

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

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

Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

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

Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. Avoid RINVOQ in patients that may be at increased risk of thrombosis.

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy *[see Adverse Reactions]*.

Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ.

Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

Vaccinations

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

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Mortality *[see Warnings and Precautions]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Abnormalities *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 1: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials

Adverse Reaction	Placebo	RINVOQ 15 mg
	n=1042 (%)	n=1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancies

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V,

decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical trials representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the two Phase 3 trials, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled trials were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were ≥1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

Adverse Reactions in Patients with Atopic Dermatitis

Three Phase 3 (AD-1, AD-2, and AD-3) and one Phase 2b (AD-4) randomized, double-blind, placebo-controlled, multicenter trials evaluated the safety of RINVOQ in patients with moderate-to-severe atopic dermatitis. The majority of patients were White (68%) and male (57%). The mean age was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. In these 4 trials, 2612 patients were treated with RINVOQ 15 mg or 30 mg orally once daily, with or without concomitant topical corticosteroids (TCS).

In the Phase 3 clinical trials (AD-1, AD-2, and AD-3), a total of 1239 patients received RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received RINVOQ 30 mg, of whom 826 were exposed for at least one year.

Trials AD-1, AD-2, and AD-4 compared the safety of RINVOQ monotherapy to placebo through Week 16. Trial AD-3 compared the safety of RINVOQ + TCS to placebo + TCS through Week 16.

Weeks 0 to 16 (Trials AD-1 to AD-4)

In RINVOQ trials with and without TCS (Trials AD-1, 2, 3 and 4) through Week 16, the proportion of patients who discontinued treatment because of adverse reactions in the RINVOQ 15 mg, 30 mg and placebo groups were 2.3%, 2.9% and 3.8%, respectively. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the RINVOQ 15 mg or 30 mg groups during the first 16 weeks of treatment.

Table 2: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg

Adverse Reaction	Placebo	RINVOQ 15 mg	RINVOQ 30 mg
	n=902 (%)	n=899 (%)	n=906 (%)
Upper respiratory tract infection (URTI)*	17	23	25
Acne**	2	10	16
Herpes simplex***	2	4	8
Headache	4	6	6
Increased blood creatine phosphokinase	2	5	6
Cough	1	3	3
Hypersensitivity****	2	2	3
Folliculitis	1	2	3
Nausea	1	3	3
Abdominal pain*****	1	3	2
Pyrexia	1	2	2
Increased Weight	1	2	2
Herpes zoster******	1	2	2
Influenza	<1	2	2
Fatigue	1	1	2
Neutropenia	<1	1	2
Myalgia	1	1	2
Influenza like illness	1	1	2

* Includes: laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
** Includes: acne and dermatitis acneiform
*** Includes: genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
**** Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalized, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, urticaria
***** Includes abdominal pain and abdominal pain upper
****** Includes herpes zoster and varicella

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 16 included anemia, oral candidiasis, pneumonia, and the adverse event of retinal detachment.

The safety profile of RINVOQ through Week 52 was generally consistent with the safety profile observed at Week 16.

Overall, the safety profile observed in patients with AD treated with RINVOQ was similar to the safety profile in patients with RA. Other specific adverse reactions that were reported in patients with AD included eczema herpeticum/Kaposi's varicelliform eruption.

Eczema Herpeticum/Kaposi's Varicelliform Eruption

Placebo-controlled Period (16 weeks): Eczema herpeticum was reported in 4 patients (1.6 per 100 patient-years) treated with placebo, 6 patients (2.2 per 100 patient-years) treated with RINVOQ 15 mg and 7 patients (2.6 per 100 patient-years) treated with RINVOQ 30 mg.

12-Month Exposure (Weeks 0 to 52): Eczema herpeticum was reported in 18 patients (1.6 per 100 patient-years) treated with RINVOQ 15 mg and 17 patients (1.5 per 100 patient-years) treated with RINVOQ 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg once daily and 251 patients received RINVOQ 30 mg once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 3 and 4, respectively.

Table 3. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N= 378 (%)	N = 719 (%)
Upper respiratory tract infection*	7	9
Acne*	1	6
Increased blood creatine phosphokinase	1	5
Neutropenia*	<1	5
Rash*	1	4
Elevated liver enzymes**	2	3
Lymphopenia*	1	3
Folliculitis	1	2
Herpes simplex*	<1	2

* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis.

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

Table 4. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	n = 245 (%)	n = 250 (%)	n = 251 (%)
Upper respiratory tract infection*	18	16	20
Increased blood creatine phosphokinase	2	6	8
Neutropenia*	2	3	6
Elevated liver enzymes**	1	6	4
Rash*	4	5	5
Herpes zoster	0	4	4
Folliculitis	2	2	4
Hypercholesterolemia*	1	2	4
Influenza	1	3	3
Herpes simplex*	1	2	3
Lymphopenia*	2	3	2
Hyperlipidemia*	0	2	2

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily
* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

Specific Adverse Reactions

Serious Infections

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (6.3 per 100 patient-years) treated with placebo, 8 patients (4.5 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (3.1 per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 0.8% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 0.8% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

Adverse Reactions in Patients with Ankylosing Spondylitis

A total of 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical trials representing 577.3 patient-years of exposure, of whom 220 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis and psoriatic arthritis. During the 14-week placebo-controlled period in Trial AS-I, the frequency of headache was 5.4% with RINVOQ 15 mg and 2.1% with placebo. During the 14-week placebo-controlled period in Trial AS-II, the frequency of headache was 3.3% with RINVOQ 15 mg and 1.4% with placebo.

Adverse Reactions in Patients with Non-radiographic Axial Spondyloarthritis

A total of 187 patients with non-radiographic axial spondyloarthritis were treated with RINVOQ 15 mg in the clinical trial representing 116.6 patient-years of exposure, of whom 31 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active non-radiographic axial spondyloarthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole and clarithromycin), which may increase the risk of RINVOQ adverse reactions. Monitor patients closely for adverse reactions when co-administering RINVOQ 15 mg once daily with strong CYP3A4 inhibitors.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg dose, 0.8 and 7.6 times the 30 mg dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MHRD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity (*see Data).*

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Report pregnancies to the AbbVie Inc.'s Adverse Event reporting line at 1-888-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg dose, 0.9 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg dose, 0.15 times the 30 mg dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg dose, 7.6 times the 30 mg dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg dose, 1.1 times the 30 mg dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations].*

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations].* Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

Pediatric Use

Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis have not been established.

Atopic Dermatitis

The safety and effectiveness of RINVOQ in pediatric patients 12 years of age and older weighing at least 40 kg with atopic dermatitis have been established. A total of 344 pediatric patients aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across three trials (AD-1, AD-2 and AD-3) to receive either RINVOQ 15 mg (N=114) or 30 mg (N=114) or matching placebo (N=116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the pediatric patients and adults. The adverse reaction profile in the pediatric patients was similar to the adults *[see Adverse Reactions].*

The safety and effectiveness of RINVOQ in pediatric patients less than 12 years of age with atopic dermatitis have not been established.

Ulcerative Colitis

The safety and effectiveness of RINVOQ in pediatric patients with ulcerative colitis have not been established.

Geriatric Use

Rheumatoid Arthritis and Psoriatic Arthritis

Of the 4381 patients treated in the five clinical trials, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical trials, a total of 274 patients were 65 years of age or older, including 34 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in patients 65 years of age and older.

Atopic Dermatitis

Of the 2583 patients treated in the three Phase 3 clinical trials, a total of 120 patients with atopic dermatitis were 65 years of age or older, including 6 patients 75 years of age. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of serious infections and malignancies in those patients 65 years of age or older in the 30 mg dosing group in the long-term trials.

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

Ankylosing Spondylitis

Of the 607 patients treated in the controlled clinical trials, a total of 32 patients with ankylosing spondylitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ankylosing spondylitis to determine whether they respond differently from younger adult patients.

Non-radiographic Axial Spondyloarthritis

Of the 313 patients treated in a phase 3 clinical trial, a total of 9 patients with non-radiographic axial spondyloarthritis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with non-radiographic axial spondyloarthritis to determine whether they respond differently from younger adult patients.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis, no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2).

For patients with atopic dermatitis, the maximum recommended dosage is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis, the recommended dosage for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment.

RINVOQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73m^2). Use in patients with atopic dermatitis or ulcerative colitis with end stage renal disease is not recommended.

Hepatic Impairment

The use of RINVOQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis, the recommended dosage for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance.

PATIENT COUNSELING INFORMATION

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

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions].*

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions].*

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

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

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions].*

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions].*

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions].*

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDS or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions].*

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions]*.

Laboratory Abnormalities

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

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations]*.

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients not to chew, crush, or split RINVOQ tablets.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, USA

Ref: 20071756 Revised: October 2022

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from the cover

Deucravacitinib

A Year in Review

Kaitlyn Bader, Senior Editor

THE FDA APPROVED DEUCRAVACITINIB (Sotyktu; Bristol Myers Squibb) for the treatment of adults with moderate to severe plaque psoriasis in September 2022.[1] Since its approval, deucravacitinib has become a necessary addition to the psoriasis armamentarium for dermatology clinicians. The allosteric TYK2 inhibitor provides patients with an oral treatment option, further helping those who may not tolerate or achieve clear skin while using topical therapies.

Deucravacitinib's groundbreaking approval was based on data from the phase 3 POETYK-PSO-1 (NCT03624127) and POETYK-PSO-2 (NCT03611751) clinical trials. Its new mechanism of action was proven efficacious compared with placebo and twice-daily apremilast (Otezla; Amgen).[1]

As deucravacitinib reaches its 1-year milestone since approval, clinicians continue to monitor deucravacitinib's real-world performance among patients and consider how it will further establish itself among available psoriasis therapies. To further discuss the importance of deucravacitinib's approval and what truly defines success, *Dermatology Times* spoke with experts in psoriasis management to provide additional insights.

Neal Bhatia, MD, is a board-certified dermatologist and the director of clinical dermatology at Therapeutics Clinical Research in San Diego, California.

Melinda Gooderham, MD, is a board-certified dermatologist, medical director at the SKiN Centre for Dermatology, and the principal investigator for the SKiN Research Centre, both in Peterborough, Ontario, Canada.

Lauren Miller, MPAS, PA-C, is a board-certified physician assistant at Southern Skies Dermatology & Surgery in Oxford, Alabama.

Q How has efficacy been maintained since the initial POETYK phase 3 trial, as well as 1 year out since deucravacitinib's approval?

Bhatia: Since the launch of deucravacitinib, I personally have seen the vast majority of patients maintain clearance after the initial month, similar to what was observed in the trials. Our site still has a few [participants] in the long-term extension trial, and they do not want to drop out [because] they have not experienced clearance with an oral therapy like this in the past. Overall, there are small areas of breakthrough that can happen with missed doses, but they are mitigated with a topical agent that the patients can use at their discretion.

Gooderham: The patients I have treated on commercial medication have been able to maintain the efficacy reached by about month 4 to 6, the latest time point since starting. I had patients in the clinical trials who have been able to maintain their efficacy for about 3 years.

Miller: The efficacy of deucravacitinib in plaque psoriasis was maintained to 52 weeks and demonstrated superiority, achieving PASI 75, PASI 90, and sPGA 0/1 in deucravacitinib vs both placebo and apremilast, the active comparator in the pivotal trials. Likewise, in POETYK PSO-LTE [NCT04036435], patients who were on deucravacitinib continuously for 2 years maintained PASI 75 response in a post hoc subanalysis. This long-term durability is critical in chronic inflammatory conditions such as plaque psoriasis.

Clinically, I have seen similar efficacy as was seen in the POETYK trials. I have seen similar efficacy both short term at the primary end point at 16 weeks and long term out to 52 weeks. I have not seen a waning of response thus far. I am optimistic my patients will maintain their efficacy consistent with [findings from] the long-term extension study.

Q What, if any, adverse events have you observed in your patients? How were they managed?

Bhatia: I have not seen anything that is worth reporting because either these patients do not come back for a year after we start them or they are managing themselves with the combination of a topical treatment for spots. These are often patients who do not want biologics or want a change to an oral therapy, plus the ease of compliance and safety without regular laboratory monitoring keeps the patients on board.

Gooderham: I did have one patient with mouth ulcers, which resolved with time, and one patient had herpes zoster in the first few months of therapy but was treated with an antiviral medication with no residual effects. Most of the patients do not report any tolerability issues at all.

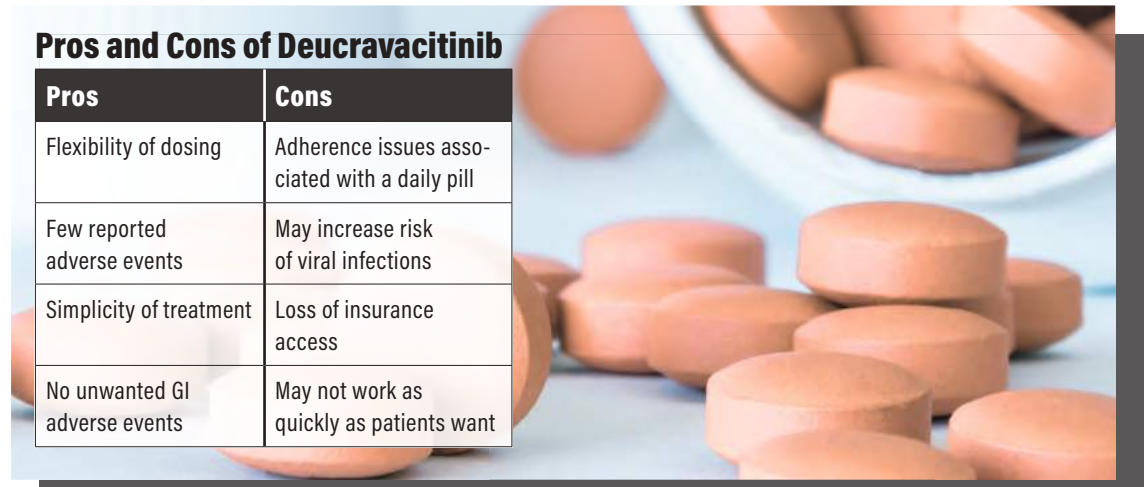
Miller: I have had a handful of patients experience acneiform eruptions. I have been able to manage the acneiform eruptions with standard topical therapy, with resolution.

Q What makes deucravacitinib different from other available psoriasis therapies, such as biologics, topicals, or oral medications?

Bhatia: Simply put, it is different because it is safe and works.

Pros and Cons of Deucravacitinib

Pros	Cons
Flexibility of dosing	Adherence issues associated with a daily pill
Few reported adverse events	May increase risk of viral infections
Simplicity of treatment	Loss of insurance access
No unwanted GI adverse events	May not work as quickly as patients want



Gooderham: Deucravacitinib is different because it is easy to take: 1 pill, once a day, no laboratory monitoring, and few tolerability issues and potential adverse effects. It's easy to travel with and can be incorporated conveniently into a daily routine. There are patients who do not want another cream and others who are reluctant to start injections, so a once-a-day pill appeals to them.

Miller: Deucravacitinib stands out among other psoriasis therapy options due to its unique mechanism of action. Unlike traditional treatments, it offers a more targeted approach. Deucravacitinib is an oral selective allosteric tyrosine kinase inhibitor (TYK2), a novel new-in-class therapy. It inhibits TYK2 via an allosteric mechanism by selectively binding to the unique regulatory domain rather than the active catalytic domain of the enzyme like other Janus kinases. It prevents activation of TYK2 and inhibits downstream signaling of IL-23, IL-12, and type 1 IFN which are implicated in a number of autoimmune diseases.

When compared with other systemic therapy, specifically its closest competitor, apremilast, deucravacitinib offers convenient, once-daily dosing and tolerability. Compared with topical therapies, deucravacitinib's systemic nature allows it to address widespread inflammation.

Q Has deucravacitinib's safety and efficacy been adequately tested in patients with skin of color?

Bhatia: The study demographics included many [participants] with darker skin types and the response rates and safety data were in line with those reported in the entire study.

Gooderham: The majority of patients in the POETYK study were white; however, in POETYK-PSO-1, as many as 20% of patients were Asian. There was very low enrollment of Black study participants (less than 2% to 4%), so there is still more to learn about the safety and efficacy of deucravacitinib across the entire skin tone spectrum.

Miller: Disparities in patients with skin of color are evident in psoriasis clinical trials as these trials often underrepresent diverse populations. This often leads to gaps in understanding treatment efficacy and safety across different skin types.

Only 2% of patients in deucravacitinib clinical trials had skin of color. However, when looking at this group, the efficacy and safety were the same as the entire trial population.

Q What considerations are different when evaluating psoriasis in patients with skin of color?

Bhatia: The most important assessment is erythema and the ability of the investigator or dermatologist to identify postinflammatory vs active violaceous erythema in darker skin. To many patients with darker skin types, the residual presence of dusky violaceous change may indicate persistence of disease, whereas in lighter skin the residual light pink to red changes are often a sign of improvement or near resolution.

Gooderham: There are many considerations in patients with skin of color, such as some

> **"Deucravacitinib stands out among other psoriasis therapy options due to its unique mechanism of action. Unlike traditional treatments, it offers a more targeted approach."**
>
> Lauren Miller, MPAS, PA-C

challenges with PASI scoring, as erythema may not be easily assessed, and this needs to be taken into consideration. Also, patients may present with more severe disease due to delays in diagnosis and less use of advanced therapies. Access can be an issue, and I hope this is addressed in some way, such as a specific trial in patients with skin of color or an access program. I also look forward to real-world evidence, perhaps from CorEvitas, that may have more diversity in patients enrolled.

Miller: Gauging the severity of lesions in patients with skin of color is known to be a difficult process. Providers need a nuanced approach when evaluating different skin tones. In patients with skin of color, erythema can appear violaceous or grey and can lead to a misdiagnosis or missed diagnosis. It can be tricky to differentiate between erythema and postinflammatory hyperpigmentation in darker skin types. Depending on the skin type, location and severity of disease can differ as well. As a provider, I must keep in mind presentation, treatment response, and potential cultural implications to provide effective care.

"Since the launch of deucravacitinib, I personally have seen the vast majority of patients maintain clearance after the initial month, similar to what was observed in the trials."
Neal Bhatia, MD

Q What real-world opinions and outcomes do you see and hear from your patients about their journey on deucravacitinib?

Bhatia: The pros are the flexibility of dosing and safety, with very few reported adverse effects, and ease of taking the tablet. The con is the need to remember to take the dose.

Gooderham: The pros of deucravacitinib in the real world that I hear from my patients are convenience and simplicity of treatment; it is better tolerated than previous oral therapies they have tried such as methotrexate, apremilast, and acitretin; and it has easier accessibility than a biologic. Some cons include that it doesn't work the same for everyone (some home runs, but some patients don't respond as well), an increased risk of viral infection (patient with herpes zoster), ongoing therapy is required, and sometimes patients lose access or insurance changes, etc.

Miller: Overall, my patients have been happy with this new therapy option. Many of my patients were taking apremilast and experienced unwanted GI adverse effects. They have not with deucravacitinib. Having another therapy option that allowed them the convenience of oral administration but without those troublesome GI issues has been greatly appreciated.

The con I've heard from patients is that deucravacitinib isn't working as quickly as they might like. But some of these patients have a history of using biologics. I set expectations with them prior to initiating therapy. However, their disease significantly impacts their quality of life. They want quick improvement in their appearance and symptoms. Biologics can offer a quicker onset of action, but some patients may not be candidates or are needle-phobic. Those patients who choose systemic therapy must be willing to sacrifice a slightly slower onset of action for the convenience of an oral therapy.

"The pros of deucravacitinib in the real world that I hear from my patients are convenience and simplicity of treatment; it is better tolerated than previous oral therapies they have tried such as methotrexate, apremilast, and acitretin."
Melinda Gooderham, MD

Q What is important for you as a clinician to see in the continued success of deucravacitinib?

Bhatia: We are all grateful to Bristol Myers Squibb for the support of the drug as well as for promoting access through specialty pharmacies and enrollment programs.

Gooderham: I would like to see some real-world data, particularly in a wider range of patients, including across the skin tone spectrum. I hope there are some access programs for patients who may have issues accessing medications. A better understanding of dermatologists that targeted TYK2 inhibition is not the same as pan-JAK inhibition so there is no reluctance to use this class of effective therapies is key for the continued success.

Miller: When looking at the success of any drug, the importance of long-term safety and durability of response cannot be overstated. As a medical professional, long-term safety data helps me provide informed decision-making, minimizing risks and adverse effects that may occur with long-term use. The durability of a therapy fosters patient trust and adherence, leading to better disease management and improved quality of life. If deucravacitinib can provide this, it will hold a key place in the treatment paradigm for patients with psoriasis. Reimbursement or access to the drug will always be critical, because a drug can be the safest and most efficacious on the market, but if my patients cannot get it, the company has failed.

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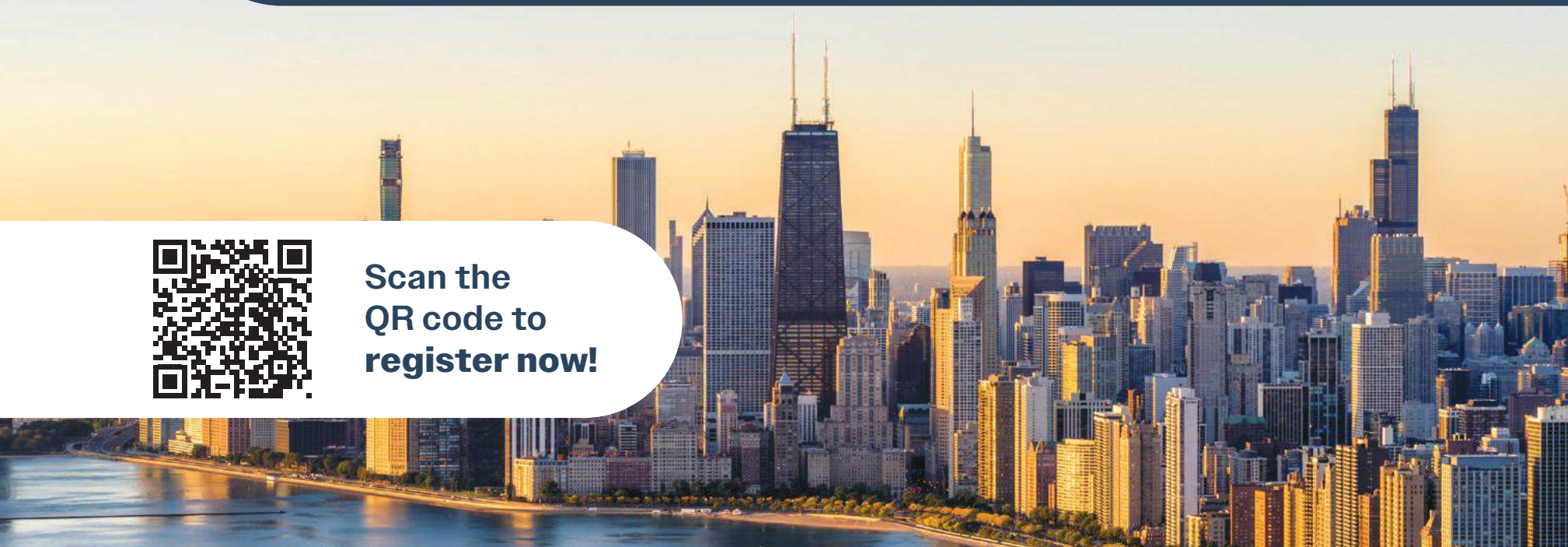

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Psoriasis
Gaps in Care

A SUPPLEMENT TO Dermatology TIMES

INSIDE

Treating All Skin Tones

By: Mona Shahriari, MD

The United States is one of the most ethnically diverse and multicultural nations in the world. While our nation continues to diversify, patients of color continue to face challenges with misdiagnosis, undertreatment, underrepresentation in clinical trials, and access to quality health care, particularly specialty care. As a dermatologist, treating patients with psoriasis—especially those from diverse backgrounds—and offering them inclusive care has always been a passion of mine.

Psoriasis has a global reach, with about 125 million patients worldwide struggling with this disease. According to the National Psoriasis Foundation, more than 8 million people have psoriasis in the US with a prevalence of 3.6% in white patients, 2.1% in Asian patients, 1.9% in Hispanic patients, and 1.5% in Black patients.[1] But these numbers may be underreported in individuals with skin of color owing to the fact that psoriasis is often misdiagnosed or overlooked in those with melanin-rich skin.

The gaps that lead to misdiagnosis and undertreatment of psoriasis in patients with diverse skin tones start at the level of medical school and residency education. Images showing skin of color are underrepresented in major textbooks as well as teaching resources, and training focusing on the nuances of treating skin disease in diverse skin tones is limited. This is compounded by the fact that skin of color is not readily seen in advertisements or public images. I challenge you to visit Google Images and search for *psoriasis*. You will see limited skin of color images, or none, depending on how far you scroll down. This limited training and exposure ultimately results in clinicians who are not proficient in diagnosing and treating psoriasis in patients with diverse skin tones.

For clinicians who are comfortable diagnosing psoriasis in patients with skin of color, further challenges exist. The language used to guide clinicians on assessing disease severity—in particular erythema—uses the word *red* a lot. Although this may work in lighter skin tones, for melanin-rich skin this language can be problematic. In darker skin tones, erythema is not always red; it can be violet, red, or even brown. For clinicians who accurately diagnose the psoriasis, their unfamiliarity with the presentation of erythema in melanin-rich skin can lead to underassessment of disease severity and undertreatment of the psoriasis. Moreover, postinflammatory pigment alteration is known to disproportionately affect our patients with skin of color and can often be more distressing than the psoriasis itself. However, these pigmentary changes are not captured in our assessments of disease severity, which may lead clinicians to dismiss or downplay their importance. Not acknowledging and treating the pigmentary changes may lead to our patients with skin of color experiencing further psychosocial burden from their psoriatic disease.

Finally, social determinants of health disproportionately affect patients with skin of color and influence health equity for these patients. Some barriers include financial stability, education, access to reliable transportation, and access to quality health care, including specialty care. All these factors can contribute to these patients' ability to receive consistent care from a dermatologist to effectively treat and manage their psoriasis.

With the continued diversification of our nation and the representation of a spectrum of diverse skin tones in our clinics, as dermatologists, it is now more important than ever to gain comfort in treating skin disease in skin of color. We need to be aware that diagnosing and managing psoriasis in patients with skin of color comes with unique challenges. It is through education on the diagnostic and treatment nuances of this disease in melanin-rich skin, awareness of the social determinants of health that affect patients with skin of color, and cultural awareness and sensitivity toward patients from diverse ethnic backgrounds that we can enable them to receive high-quality health care in an inclusive society that recognizes them for their unique selves.

More than 8 million people have psoriasis in the US with a prevalence of

3.6%	2.1%	1.9%	1.5%
in white patients	in Asian patients	in Hispanic patients	in Black patients

These numbers may be underreported in individuals with skin of color owing to the fact that psoriasis is often misdiagnosed or overlooked in those with melanin-rich skin.

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VISIBLE Study Paves Way for More Equitable Psoriasis Research

The study is the only large-scale dermatologic study to prospectively generate insights into skin conditions among patients of racial and ethnic minority groups.

By: Emma Andrus,
Assistant Editor

DESPITE EXTENSIVE STUDIES and an ever-expanding treatment landscape in psoriasis, there is a significant gap in research related to the impact and manifestations of the condition in patients with skin of color who belong to racial or ethnic minority groups. Through exploring the distinct clinical presentations, impacts on quality of life, disparities in health care, and cultural stigmatization experienced by this patient population, Janssen's VISIBLE study (NCT05272150)[1] serves as a call to action for dermatology providers and investigators to continue to bridge these gaps in research and care.

The phase 3b, double-blind, multicenter, placebo-controlled, randomized clinical study is the first of its kind and the only large-scale demographic study to prospectively generate insights into skin conditions among patients of racial and ethnic minority groups.

The study also seeks to evaluate

the safety and efficacy of guselkumab (Tremfya) compared to a placebo in patients with skin of color who present with a moderate to severe plaque or scalp psoriasis diagnosis. Participants self-identified as either non-white or non-Caucasian and have had a psoriasis diagnosis for at least 6 months prior to treatment initiation.

Janssen announced initiation of the groundbreaking study in March 2022[2] as one of several components of the company's commitment known as ORTHE, or Our Race to Health Equity. According to Janssen, while guselkumab has a well-established profile of efficacy and safety in psoriasis treatment, there are limited data on the use of the drug in patients of minority populations. In fact, within the previous 2 decades, 86% of phase 3 clinical trials investigating psoriasis treatments have included a majority of white participants.[2]

Andrew Alexis, MD, MPH, is a professor of clinical dermatology and vice chair for diversity and inclusion at Weill Cornell Medicine in New York, New York, and the study's lead investigator. Alexis is also president of the Skin of Color Society and director of the first-of-its-kind Skin of Color Center at Weill Cornell Medicine. According to Alexis, VISIBLE is poised to shed light on several relevant clinical questions related to treating the condition in diverse patient populations.

"In addition to common assessments of disease severity such as PASI [Psoriasis Area and Severity Index] and IGA [Investigator's Global Assessment], the study includes novel secondary end points that are particularly relevant to patients with skin of color, such as the assessment of pigmentary alterations associated with psoriasis," he said. "For the first time, we can evaluate the safety and efficacy of a biologic treatment for psoriasis in a patient population that has historically been underrepresented in clinical trials of psoriasis."

The study has not been without challenges.

"Some of the challenges faced by a study like VISIBLE include the nuances of performing investigator assessments such as PASI and IGA in patients with richly pigmented skin, among whom rating of erythema can be more challenging due to the optical effects of increased melanin pigment. This challenge was overcome by robust investigator training modules and use of confirmatory review of photographs with both standard and polarized lighting," Alexis said. "Another challenge overcome by the VISIBLE study was the enrollment of patient populations that have historically faced access barriers to clinical trials. This was addressed by broadening the range of study sites and investigators to ensure geographic and demographic diversity."

Alexis is hopeful the study will improve dermatology providers' understandings of identifying psoriasis in darker skin types.

"The VISIBLE study will broaden our understanding of the range of clinical features (at baseline and over the course of treatment) in patients with skin of color," he said. "This in turn will help to improve the quality of care we provide to our patients."

Disclosure: Andrew Alexis, MD, MPH, is a paid consultant for Janssen.

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Skin of Color Resources for Clinicians

National Psoriasis Foundation

The National Psoriasis Foundation provides an abundance of information for clinicians and patients.

The Skin of Color Resources for Health Care Providers offers podcasts, webinars, and videos to help clinicians recognize, diagnose, and manage psoriasis in patients with skin of color.

In this webinar, Tiffany Mayo, MD, discusses the features of psoriasis, the challenges affecting diagnosis, treatment options, and tips for treating patients with skin of color.

In this podcast, Mona Shahriari, MD, shares how psoriasis presents in skin of color, the potential for misdiagnosis, cultural beliefs, and more, to help all clinicians provide the best care for this population.

RheuMuseum

RheuMuseum is an interactive site with tours, videos, and guidelines to help clinicians treat patients with psoriatic arthritis. The innovative site covers comorbidities, clinical manifestations, and other critical information.

Skin of Color Society

The Skin of Color Society website provides information for clinicians and patients about many skin conditions, from acne to vitiligo, and has a section devoted to psoriasis. Clinicians can find resources including textbooks, videos, blog articles, and more to offer guidance in treating patients with skin of color.

Skin of Color Resource for Clinicians to Share With Patients

Global Healthy Living Foundation

Global Healthy Living Foundation provides many resources to those living with psoriasis and psoriatic arthritis. Providers can direct patients to the helpful features, which include patient guides and information on how to get involved in studies of psoriasis. The Black, Indigenous, People of Color (BIPOC) Patient Voices page focuses on patients with skin of color living with psoriasis or psoriatic arthritis.

Accurately Recognizing and Diagnosing Psoriasis in Patients With Skin of Color

By: Nicole A. Negbenebor, MD

PATIENTS OF ALL DIVERSE ETHNIC BACKGROUNDS are affected by psoriasis. There may be delays in diagnosis and treatment of psoriasis in patients with darker skin tones due to the clinical presentation variations and less visible erythema. Some features of psoriasis in darker skin types may also be mistaken for other papulosquamous disorders because they share similar characteristics. Research shows that patients with undiagnosed psoriasis are more likely to have skin of color.[1] This article provides a practical checklist to help guide health care professionals in accurately identifying and diagnosing psoriasis in patients with skin of color.

Nicole Negbenebor, MD, is a Mohs micrographic surgery and cutaneous oncology fellow in the University of Iowa's Department of Dermatology.

Clinical variations include the following:

- ✓ Patients may have increased postinflammatory hyperpigmentation or hypopigmentation in areas of previous skin involvement. These patches and macules of dyspigmentation are due to inflammation altering the production of melanin.[2] Depending on the severity and location, these patches and macules may resolve within a few months to a year. Providers should be aware that patients can be most bothered by the dyspigmentation and that this may be the chief complaint rather than one about the psoriasis itself.[2,3]
- ✓ Erythema may be more subtle or appear hyperpigmented, gray, and/or violaceous. This may lead to a lower overall PASI score (Psoriasis Area and Severity Index) since the erythema can present with a darker hue in patients with darker skin tones. Providers need to be aware that the violaceous or hyperpigmented hues can be a sign of ongoing inflammation rather than postinflammatory hyperpigmentation.[2-4]
- ✓ Overlapping papulosquamous conditions that could mimic psoriasis include cutaneous lupus erythematosus, sarcoidosis, cutaneous T-cell lymphoma, pityriasis versicolor, and lichen planus. Patients should have a full body skin examination, including the nails and scalp, to help with diagnosis of psoriasis. A biopsy may be needed for confirmation.[5]
- ✓ Because of delays in care, patients with skin of color may initially present to the clinic with a greater body surface area affected.[6]
- ✓ Scale may be thicker or more severe in patients with hair textures that do not allow for frequent hair washing. Buildup of scale can be more prominent throughout the scalp.[7] Research shows that Black and Asian patients are more likely to have scalp psoriasis.[7]
- ✓ Asian and Hispanic patients can present more frequently with pustular psoriasis. Asian patients are also more likely to have inverse psoriasis and develop erythrodermic psoriasis.[8,9]

In conclusion, it is imperative that health care professionals accurately recognize and diagnose psoriasis in patients with skin of color. This requires a comprehensive understanding of the unique clinical variations that patients can present with for psoriasis. By leveraging this checklist, health care professionals can improve care for patients of diverse racial and ethnic backgrounds. This will provide effective and timely management of psoriasis in patients with skin of color and minimize delays in diagnosis.

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Confronting Racial Disparities in Dermatologic Education

By: Kaitlyn Bader, Senior Editor

Including the accurate representation of all skin types in dermatologic education has never been more important for patient care, as the Skin of Color Society predicts that more than 50% of the US population will include those with skin of color by 2042.[1]

"There has been an infinite growth in materials, photographs, textbooks, and discussion around dermatologic disease in skin of color. There was only one direction to go: Up!"
Christopher Bunick, MD, PhD

In 2020, researchers reported in *Clinics in Dermatology* that dermatology was the second least-diverse medical specialty (behind orthopedic surgery), which contributes to a lack of support for patients with skin of color.[2] In 2021, Narla et al published a review of racial disparities in dermatology in *Archives of Dermatological Research* that addressed the lack of skin of color representation in education. The authors cited a review of 4146 textbook images from 4 general preclinical anatomy books commonly assigned at popular medical schools and found that only 4.5% of images represented patients with skin of color.[3]

Despite the previous lack of representation in educational materials, large-scale efforts have been made in recent years to positively change these statistics. The American Academy of Dermatology's Skin of Color Curriculum includes a "definitive inpatient and outpatient curriculum for the diagnosis and effective treatment of skin of color disease and conditions for practicing dermatologists and dermatology residents."[4] The Skin of Color Society lists numerous resources on its website for physicians and students, including recommended skin of color textbooks, educational videos, a list of ethnic skin centers in the US, and mentorship opportunities.[5]

To further discuss the changing landscape of skin of color representation in dermatology, Christopher Bunick, MD, PhD, and Shawn Kwatra, MD, review how they have seen representation change in their own experiences.

Christopher Bunick, MD, PhD, is a physician-scientist and an associate professor of dermatology at the Yale School of Medicine in New Haven, Connecticut.

Shawn Kwatra, MD, is an associate professor of dermatology at Johns Hopkins University School of Medicine and the director of the Johns Hopkins Itch Center in Baltimore, Maryland.

Q When you were in medical school, were dermatologic conditions in patients with skin of color (including Black, Pacific Islander, Asian, Hispanic, and Native American individuals) accurately depicted?

Bunick: In many medical schools, dermatology exposure can be rather limited. I had about 1 week of dermatology training in my first and second years medical school and a 1-month elective in early fourth year. To a medical student, dermatology is a foreign language, and one is just trying to master what a macule or papule is. Learning the primary lesions and a few common diseases was the emphasis, not different presentations of dermatologic conditions in patients with skin of color. Therefore, training at this stage of career to my recollection did not focus on or address skin of color directly. I honestly think I gained the most knowledge recognizing different clinical presentations in skin of color my first year or two out of residency. I have always felt the learning curve the first year as an attending is greater than all the years of medical school and residency combined. Nothing compares to learning from the patients you care for—and the thing about dermatology is you continue to learn from every patient every day.

Kwatra: In medical school, we only had a few days dedicated to dermatology. At the time, there were not as many available images of patients from diverse patient populations. Since then, there have been big efforts made by many in our field to make more diverse and inclusive skin atlases of dermatologic conditions. I gained the most knowledge at my own clinical practice as an attending in Baltimore, Maryland, which is one of the most diverse areas of the country. Through my own clinical practice, which is focused on itch, I have seen a lot of differences in how pruritic skin disorders such as prurigo nodularis and atopic dermatitis present uniquely in patients with skin of color. For example, atopic dermatitis in Black patients presents with more extensor and papular involvement. Prurigo nodularis in Black patients will often present with more fibrotic nodules.

Q How have you seen the inclusion of patients with skin of color in educational and training materials change from your time as a student to now?

Bunick: There has been an infinite growth in materials, photographs, textbooks, and discussion around dermatologic disease in skin of color. There was only one direction to go: Up! I believe this has increased the competency of all dermatologists to recognize and help patients. We are a visual specialty first, data- and pathology-driven specialty second. Therefore, it starts with seeing over and over examples of skin problems in patients of various backgrounds. Education that enhances our initial ability to diagnose and converse with patients in a caring and intelligent manner is important for the overall patient experience.

Kwatra: Over the past several years there have been great efforts by leaders in our field to put together skin atlases from diverse patient populations. We are improving.

Q As a professor, how do you teach students about the importance of accurate representation, specifically in patients with skin of color with psoriasis?

Bunick: Clinical exam is vitally important. The first impression you have of a patient is always based on pattern recognition, your memory bank or recollection of how diseases have looked in all the patients you have cared for or studied in a textbook. In sports, coaches always emphasize *the fundamentals* or *the basics* as keys to success. This is no different in dermatology; our fundamentals are morphology, distribution, symmetry, temporal relationships, modifying factors, etc. Therefore, I teach thinking about the fundamentals over and over, performing exams consistently the same way to reduce omissions or errors, and smartly utilizing laboratory and pathologic examination along with HPI to complement your physical exam. In patients

"Patients with skin of color with psoriasis often have less obvious erythema or redness that may appear violaceous or hyperpigmented in color."
Shawn Kwatra, MD

with skin of color, moderate to severe psoriasis is much easier to diagnose, in my opinion, than the mild cases. Milder disease tends to mimic other skin conditions more readily, making it vital to pay attention to fundamental details.

Kwatra: I teach students that erythema or redness is less easily appreciable in patients with skin of color. So we use more objective measures, such as itch intensity, to help in assessing disease severity.

Q Are there any resources that you rely on or recommend?

Bunick: I agree with all the recommendations and materials provided by the AAD and Skin of Color Society.

Kwatra: I often times use the worst-itch rating scale, or WI-NRS, to ask patients—on a scale of 0 as no itch to 10 as the worst imaginable itch—what is the worst itch that they have had over the preceding 24 hours as an objective measure.

Q As a physician, what key differentiating clinical presentations of psoriasis are you looking for when diagnosing and treating patients with skin of color?

Bunick: When it comes to the appearance of psoriasis plaques, the common pink to red color seen in lighter skin tones may appear more gray or brown in skin of color. This can also affect the scale, which may appear darker as well. Resolved plaques more commonly leave postinflammatory hyperpigmentation [in skin of color] than in lighter skin. But the ability of plaques to present on symmetric locations, such as elbows and knees, is the same, and that pattern recognition is important to diagnosis, as is evaluating the scalp, genitals/buttocks, and nails for clues to psoriasis. All patients with potential psoriasis should be asked about joint pains due to psoriatic arthritis. When in doubt about whether it is truly psoriasis, compared with atopic dermatitis or nummular eczema, for example, then a skin biopsy can be very helpful for diagnosis. Definitive diagnosis is important if a provider is considering a biologic or systemic therapy.

Kwatra: Patients with skin of color with psoriasis often have less obvious erythema or redness that may appear violaceous or hyperpigmented in color. Postinflammatory hypo- and hyperpigmentation are common as well.

Other key presentations I look for include the following:

- Less conspicuous erythema that may appear violaceous or hyperpigmented
- Postinflammatory hypo- or hyperpigmentation
- Potential clinical mimickers of psoriasis, such as lichen planus (especially hypertrophic type) or cutaneous lupus erythematosus (discoid and subacute)
- Potential increased area of involvement/BSA at initial presentation
- Scalp psoriasis in Black individuals, including the impact of hair texture, styling practices, and washing frequency on selection of topical therapy and severity
- Potential traditional/cultural therapies used before seeking a dermatological consultation

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GRAPPA Continues Efforts to Advance Care for Patients With Plaque Psoriasis

By Heather Raglin, MS, Editor

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is dedicated to furthering clinical care, education, and research for patients with psoriasis and psoriatic arthritis. The interdisciplinary organization brings together rheumatologists, dermatologists, basic scientists, medical and research trainees, and patient research partners.

The organization recently celebrated 20 years of helping develop medical guidelines for the treatment of psoriasis and psoriatic arthritis. GRAPPA also educates practitioners on new developments in the field and funds research grants to advance medical knowledge of psoriasis and psoriatic arthritis.

"The impetus for forming GRAPPA was (and remains) to take advantage of the many new therapeutic agents and treatment approaches for psoriatic arthritis and psoriasis to bring together diverse expertise to help explore ways to improve outcomes for affected patients," said Arthur Kavanaugh, MD, professor of medicine at the University of California at San Diego. He continued, "Since its formation, GRAPPA has helped advance the field by producing treatment recommendations for [psoriatic arthritis], developing novel research studies, supporting research, and assisting in educational programs."

GRAPPA's goals include providing an opportunity for clinicians to share knowledge and research findings, to promote the development of national and international collaborative registries of patients to standardize data, and to promote public awareness of psoriasis and psoriatic arthritis. "We are excited to see an expansion of the types of research being performed, including clinical research, translational research, and basic science research," GRAPPA Research Committee Co-chairs Vinod Chandran, MD, DM, PhD, MBBS, FRCPC, associate professor, Division of Rheumatology, Department of Medicine at the University of Toronto, and director of the Psoriatic Arthritis Program, Schroeder Arthritis Institute at the University Health Network; and Wilson Liao, MD, professor and vice chair of research in the Department of Dermatology at the University of California, San Francisco, told *Dermatology Times*.

They added, "Special topics of interest include developing better ways to diagnose psoriatic arthritis, understanding the full spectrum of psoriatic diseases, refining outcome measurement tools, identifying novel molecular and digital biomarkers, understanding sex and gender differences, and examining best practices for managing difficult-to-treat patients. We are excited that many of these research activities are being supported by the collaborative efforts of academia, industry, nonprofit organizations, and patient research partners."

GRAPPA also collaborates with other professional organizations, such as the American Academy of Dermatology and the American College of Rheumatology, to further knowledge of research within those specialties. In addition, the group works closely with representatives of member biopharmaceutical companies on research on effective therapies and promotes public awareness of psoriasis and psoriatic arthritis.

GRAPPA offers video training modules to support clinicians in learning examinations such as the Psoriasis Area and Severity Index and Nail Psoriasis Severity Index. The nonprofit organization is based in Seattle, Washington, and has more than 1000 members from around the world. ■

JOURNAL DIGEST

The Latest in Dermatologic Studies

Kaitlyn Bader, Senior Editor

Dermatology Times' newest website series, "Journal Digest," features a weekly collection of trending studies from top dermatologic journals. In case you missed it, last month's installment included studies on secukinumab for erythrodermic psoriasis in children, updated surgical guidelines for early-stage vulvar squamous cell carcinoma, upcoming hand eczema treatments, and more.

European Journal of Dermatology

Machine Learning Algorithm to Predict Response to Immunotherapy in Real-Life Settings for Patients With Advanced Melanoma

According to Frenard et al, "defining relevant biomarkers to predict treatment outcome based on immune checkpoint inhibitors (ICIs) is needed in order to increase overall survival of metastatic melanoma (MM) patients." In their study, Frenard et al compared different machine learning models' ability to identify biomarkers from clinical diagnoses and follow-ups of patients with MM to predict treatment responses to ICIs. The Random Forest database showed the highest scores of accuracies (0.63) and sensitivity (0.64), with additional high scores for precision (0.61) and specificity (0.63).

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Clinical, Cosmetic, and Investigative Dermatology

Treatment of Erythrodermic Psoriasis in Children With Secukinumab: A Case Report

In a recent case report of secukinumab for erythrodermic psoriasis in pediatric patients, Lu et al presented a case of a patient aged 7 years who transitioned from generalized pustular psoriasis to erythrodermic psoriasis after routine systemic treatment. After treatment with secukinumab, the symptoms improved within 48 hours after the first injection, and lesions almost completely cleared after the fifth injection. Between April and October 2022, the patient completed 11 doses of secukinumab, achieved PASI 100, and had no adverse reactions. Lu et al noted that although the efficacy of secukinumab in pediatric patients with erythrodermic psoriasis is unknown, their recent case report suggests that secukinumab may be effective.

Reference

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Experimental Dermatology

Altered Structure Indicating Reduced Barrier Function of Lesional Compared to Non-Lesional Psoriatic Skin

Zolotas et al molecularly compared lesional psoriatic skin (LPS) with nonlesional psoriatic skin from 19 patients noninvasively in vivo, using confocal Raman microspectroscopy. The authors noted that previous studies show a higher transepidermal water loss, lower hydration, and abnormal concentration and composition of intercellular lipids, as well as alterations in secondary keratin structures in the psoriatic stratum corneum. The findings showed a lower total lipid concentration, a shift of lamellar lipid organization toward more gauche conformers, and an increase of the less dense hexagonal lateral packing of the intercellular lipids in LPS."

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Journal of Cutaneous Medicine and Surgery

A Review of Existing and New Treatments for the Management of Hand Eczema

To distinguish what therapies are available for the treatment of hand eczema, Ho et al conducted a literature review by searching for the terms *hand eczema* and *hand dermatitis* in PubMed, CENTRAL, and Embase. To identify new and upcoming therapies, Ho et al searched for the terms *hand eczema*, *hand dermatitis*, *atopic dermatitis*, and *vesicular eczema of the hands and/or feet* through ClinicalTrials.gov from 2000 to 2022. There were 56 ongoing clinical trials identified for pharmacological treatments for hand eczema from 2000 to 2022, with 16 new or ongoing. Some upcoming treatments identified are lebrikizumab, delgocitinib, gusacitinib, tofacitinib, fezakinumab, etokimab, tezepelumab, and JNJ-39758979.

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International Journal of Dermatology

Extensive Ecchymotic Patch in a Patient With Chronic Lymphocytic Leukemia

Guenther et al reviewed a case of a female patient aged 68 years with a history of chronic lymphocytic leukemia and an extensive focal purpuric patch formed by a confluence of smaller purpuric patches and present for 4 months. The patient had been treated with bendamustine and rituximab 4 years prior and began treatment with acalabrutinib 5 months prior to presentation when her white blood cell count rose to 147 k/µl. The patient was not on anticoagulants or antiplatelet agents at the time, but the purpuric patch persisted for 4 months and was asymptomatic. A punch biopsy was taken from the left forearm and sent for histopathologic examination, which revealed acalabrutinib toxicity.

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Guenther J, Vecerek N, Worswick S. Extensive ecchymotic patch in a patient with chronic lymphocytic leukemia. *Int J Dermatol*. Published online August 7, 2023. doi:10.1111/ijd.16801

Journal of Dermatologic Science

Detection of a Natural Antibody Targeting the Shed Ectodomain of BP180 in Mice

According to Mai et al, pemphigoid diseases are characterized by subepidermal blister formation accompanied by autoantibodies targeting skin component molecules like BP180. In their study, the authors immunized mice with full-length mouse BP180 (mBP180) to produce anti-mBP180 antibodies. Mai et al analyzed the characteristics of the anti-mBP180 antibodies in terms of epitopes, immunoglobulin subclasses, and somatic hypermutations. The investigators found "monoclonal anti-mBP180 [shed ectodomain] antibodies react to neoepitopes on the 13th collagenous region of cleaved mBP180, which corresponds to the epitopes of linear IgA bullous dermatosis antibodies in human BP180" and that "mice potentially have natural antibodies targeting the neoepitopes of cleaved mBP180 EC."

Reference

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American Journal of Clinical Dermatology

Comorbid Conditions Associated With Alopecia Areata: A Systematic Review and Meta-analysis

To better understand the comorbidities of alopecia areata (AA), Ly et al performed a systematic review and meta-analysis using PubMed, Embase, and Web of Science for case-control, cross-sectional, and cohort studies.

There were 3428 abstracts and titles screened, and 345 full-text articles were reviewed. In total, 102 studies were selected, which included 680,823 patients with AA and 72,011,041 healthy controls. Among patients with AA, comorbidities with the highest odds ratios compared with healthy controls and data available from more than 1 study included vitamin D deficiency, systemic lupus erythematous, vitiligo, metabolic syndrome, and Hashimoto thyroiditis.

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Ly S, Manjaly P, Kamal K, et al. Comorbid conditions associated with alopecia areata: a systematic review and meta-analysis. *Am J Clin Dermatol*. Published online July 18, 2023. doi:10.1007/s40257-023-00805-4

clinical insights

Navigating Topical Steroid Withdrawal and Extreme Adverse Reactions to Corticosteroids

Emma Andrus, Assistant Editor

As more topical treatments have entered the dermatology space over the years,[1] topical steroid withdrawal (TSW), also known as red skin syndrome or topical steroid addiction, has led to widespread discussions about the potential implications of the prolonged use of topical corticosteroids.

Despite the tremendous impact of TSW, little is known about the effects of TSW, including how frequently it arises in patients, and there is limited research[2] exploring this multifaceted and extreme corticosteroid reaction.

Understanding TSW

TSW, which can be painful and debilitating in nature, can lead to burning, erythema, flaking, swelling, thinning, and wrinkling of the skin. Nodules, papules, and pus-filled bumps, which are susceptible to oozing, can occur. Aside from physical components of TSW, patients may also experience depression, fatigue, hair loss, insomnia, and shivering.[2]

In fact, this burden of morbidity is often compounded by dismissal from health care providers. An April 2023 retrospective review examined the implications of TSW symptomology, management, and patient impacts. As a result, many patients reported being dismissed by dermatology providers.[3]

Prevention Best Practices

Peter Lio, MD, is a clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine and the founding director of the Chicago Integrative Eczema Center.

"I think the first thing is just basic, well-accepted, sensible use of the medicines," Lio said. "I truly think that a lot of the people that I look to and trust that I think are great clinicians. Some of them have said, 'I really don't see this condition,' and my interpretation is not that they're lying, or that they're trying to deceive anybody, but that literally, if you do a really good job with steroids, and you're paying attention, this should be really, really rare."

According to Lio, most cases of TSW tend to happen when patients make changes to their topical steroid routine, such as repeated refills or increased quantities and potencies. However, Lio said the discussion has now turned to the possibility of small amounts of topical steroids leading to the development of TSW.

"I do have patients who really have not used a lot—in my opinion, haven't overused [topical steroids]—but really do appear to have this TSW syndrome," Lio said.

Management Strategies

If a patient presents with TSW, Lio said the primary concern should be trusting and listening.

"I think some of the best things we can do are very much the same things we would do for eczema, atopic dermatitis, without steroids," Lio said.

Lio recommended considering the following treatment and relief options for patients with TSW:

- Coal tar
- Cooling treatments
- Cyclosporine
- Dupilumab
- JAK inhibitors abrocitinib and upadacitinib
- Phototherapy
- Wet-wrap therapy
- Zinc

Patient Support and Education

When it comes to education on TSW, the relationship between provider and patient understandings of the condition almost go hand in hand. Due to the limited research and lack of consensus on the effects and diagnosis of TSW among dermatology clinicians and providers, patients are often led to seek assistance from sources online, which may not be reputable and ultimately may further exacerbate the burden of TSW.[2]

"One path is to just sort of try to push back and educate and say, 'Listen, it's unlikely. Let's still do this.' I think that can be reasonable in the right situation," Lio said. "One option is to sort of roll your eyes and dismiss people. I think that's always a bad choice. I don't think that's just, good medicine. That's not a good patient-doctor relationship."

Lio said it is important to emphasize to patients that in the treatment of dermatologic conditions that there is not always one clear truth or answer. As someone who has worked closely with patients who have been affected by steroid use and overuse, Lio recommends a third approach, which entails presenting TSW education at face value.

"I tend to say: 'Listen, even if we don't think that's what's going on now, I can work with you,'" Lio said. "Thankfully, I feel very lucky that we now have a whole host of nonsteroidal treatments. So I can say, 'All right, let's assume you have it or [are] at risk for it. Let's just avoid steroids as best we can.'"

In some instances, such as life-threatening anaphylaxis or vasculitis in response to nonsteroidal options, Lio said it is important to inform patients ahead of time that a steroid treatment may be necessary. However, it is equally as important to emphasize that this is not always an absolute contraindication and that nonsteroidal options can still be potential options for treatment in the future.

Future Directions

Currently, there is no consistent diagnostic criteria applicable for the clinical diagnosis of TSW.[1]

"Part of the problem is that we don't have a great diagnostic criteria. It's like we don't really have a ICD [International Classification of Diseases] code for it. We don't have criteria, and I've been working on that," Lio said.

Moving toward the future, Lio said that growing patient understanding of TSW is likely to pave the way for future consensus and guidance for the condition.

"Most of the patients I see, unlike anything else I've seen in dermatology, almost all the patients with TSW come in telling me they have TSW," he said. "I think it's fascinating, I think it's worth thinking about together."

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Skin Reactions Can Be Traced Back to PPE Use

Researchers found that use of personal protective equipment could be associated with skin problems; however, protective applications reduced these issues.

Emma Andrus, Assistant Editor

The use of personal protective equipment (PPE) in intensive care units (ICUs) contributed to a wide range of skin-related problems during the COVID-19 pandemic, according to a study[1] published in *Nursing in Critical Care*.

Investigators sought to identify common skin problems caused by the use of PPE, citing prior studies indicative of skin problems caused by wearing goggles, gowns, or masks in health care settings. They note that these problems may have been exacerbated by the length of time PPE was worn in order to prevent and control infection.

They first began by referencing meta-analyses outlining the most common skin problems associated with the use of the most common forms of PPE. Regarding the use of face shields, goggles, and N95 masks, common skin concerns included acne, allergic dermatitis, dry skin, pressure sores, rash, desquamation, dryness, tightness, and erythema. Wearing gloves could be attributed to allergic contact dermatitis, acne, chapped skin, eczema, seborrheic dermatitis, skin discoloration, and skin thickening. When using gowns or coveralls, health care professionals face acne, dry skin, pruritus, and rash.

In order to identify the skin concerns specific to 3 COVID-19 ICUs in a single study hospital located in Altındağ, Turkey, researchers conducted a cross-sectional survey. Intensive care unit workers were asked the following questions:

What was the proportion of the development of skin problems related to using PPE?

Did the development of skin problems related to using PPE differ according to the sociodemographic characteristics of the nurses?

Did the development of skin problems related to using PPE differ according to the working conditions in the COVID-19 ICU?

Did the development of skin problems related to using PPE differ according to protective applications to prevent skin problems?

Retrospective data were collected from 82 intensive care nurses who had worked between December 2021 and June 2022. These nurses were required to actively provide care in COVID-19 ICUs while using Level 3 PPEs, including bonnets, boot/shoe covers, face shields, gloves (elbow-length), goggles, gowns/coveralls, and medical masks. They completed the online survey and sent in optional photographs of skin problems or conditions related to PPE wear.

Of these participants, 90.24% reported the presence of any skin-related problem caused by PPE use. The 3 most common skin problems associated with PPE wear included an N95 mask (in 89% of respondents), goggles (in 79.3% of respondents), and face shields (in 34.1% of respondents). The 4 most common skin problems included acne, pressure sores, regional pain, and skin reactions, which included allergic contact dermatitis and contact urticaria.

Pressure sores were the most common skin concern associated with use of goggles, N95 masks, bonnets, gloves, boot/shoe covers, and gowns/coveralls. Use of face shields was most frequently associated with regional pain. Approximately 90.24% of nurses reported experiencing at least 2 or more skin problems due to PPE use.

Researchers also evaluated protective applications of certain aids to prevent skin problems associated with PPE use. The most common forms of protection included pressure-reducing surfaces, transparent dressings, thin hydrocolloid dressings, and protective pomades. Some correlations could be made between protective applications and skin concerns.

The proportion of nurses who reported experiencing pressure sores was significantly lower in instances where protective applications were used as opposed to those who did not use any protective applications prior to or during PPE use. Skin reactions were also lower among nurses using protective applications when wearing gloves and boot/shoe covers. Greater prevalence of skin problems was associated with nurses wearing bonnets and face shields who did not use protective applications.

However, protective applications also led to increased skin concerns in some cases. For example, an increase in regional pain could be linearly associated with an increase in protective applications among those wearing N95 masks.

"The results of this study provide preliminary data for modifying or developing PPEs that minimize harm," according to Altin et al. "In this current study, each of the Level 3 PPEs used in the pandemic caused skin problems. Nine of 10 nurses had skin problems associated with PPE. In preparation for future pandemics, it would likely be beneficial to design a work program that does reduce the use of PPE in clinics to prevent skin problems. In addition, effective protective applications can be a temporary solution to prevent skin problems. However, there is a need for the development of PPE that does not cause skin problems for a definitive solution."

Reference

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Sherry Young/Stock.Adobe.com

Are You Counseling Your Patients With HS About Proper Wound Care?

A survey found that more than half of clinicians do not discuss clothing modifications, and half report providing patients with wound care supplies that are covered by insurance.

Emma Andrus, Assistant Editor

As many as one-third of surveyed dermatologists reported that they do not counsel their patients with hidradenitis suppurativa (HS) on wound care.

In one study,[1] investigators sought to evaluate the frequency and importance of wound care counseling or product recommendations for patients with HS. They noted that wound care is an unmet need of the condition due to the presence of acute flares and chronic, draining wounds.

Researchers distributed an anonymous online questionnaire via an email listserv to board-certified and actively practicing dermatologists in the United States between August 2022 and October 2022. It consisted of multiple-choice questions related to HS, wound care, at-home management, clothing modifications, and more.

In total, 50 dermatologists completed the questionnaire. Of these, 38% self-identified as experts in HS.

When asked about their current counseling practices for patients with HS, 90% of surveyed dermatologists agreed that patients with HS are in need of greater education regarding wounds and wound care methods. Furthermore, 70% said they believe patients with HS lack education on wound care best practices.

Despite this, just over 1 in 4 surveyed dermatologists said they do not counsel their patients about managing acute flares at home. Even still, more than half, 52%, reported that they do not counsel patients about clothing modifications, and nearly 1 in 3 said they do not discuss wound care dressings with their HS patients. Half of respondents (n = 25) said they order wound care supplies for patients with HS that are covered by insurance.

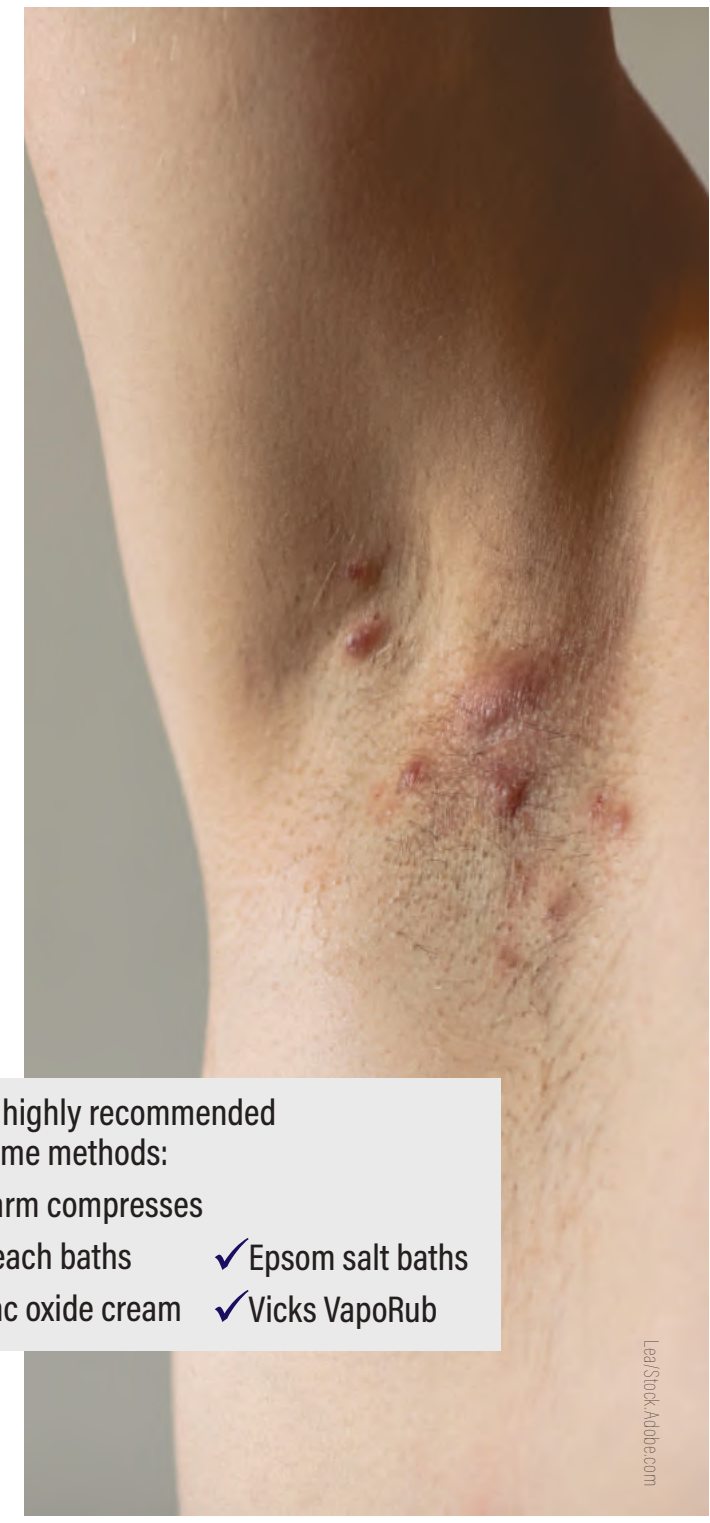
Additionally, researchers examined dermatologists' perceptions of the efficacy of several topical agents, including bleach baths, warm compresses, and more.

Of the surveyed dermatologists, the most commonly recommended dressings were abdominal pads, gauze, and panty liners/menstrual pads, whereas the most highly recommended at-home methods of management included use of warm compresses, bleach baths, zinc oxide cream, Epsom salt baths, and Vicks VapoRub.

Of these recommended dressings and management tools, dermatologists ranked warm compresses, bleach baths, and Epsom salt baths as the most highly effective management tools for patients with HS, according to perceived efficacy.

Potential study limitations include a low sample size and proportion of nonacademic dermatologists.

"There are numerous wound care supply companies across the United States that will distribute supplies to patients that are partly or completely covered by insurance. Typically, these orders require documentation of wound size and location in the clinical note and specific requests for supplies.... Referrals to wound care can also be beneficial in increasing patient access to wound care supplies. Having access to a variety of dressings has been shown to improve patient quality of life by reducing pain, odor, and staining of clothes," according to Poondru et al. "These findings underscore areas for improvement in wound care education for patients with HS."


Lea/Stock.Adobe.com

Most commonly recommended dressings:
- ✓abdominal pads
- ✓gauze
- ✓panty liners/menstrual pads

Most highly recommended at-home methods:
- ✓warm compresses
- ✓bleach baths
- ✓Epsom salt baths
- ✓zinc oxide cream
- ✓Vicks VapoRub

Reference
1. Poondru S, Scott K, Riley JM. Wound care counseling of patients with hidradenitis suppurativa: perspectives of dermatologists. *Int J Womens Dermatol.* 2023;9(3):e096. doi:10.1097/JW9.0000000000000096 ■

Addressing Misconceptions, Concerns Around Biosimilar Use

Laura Joszt, MA, Correspondent

Research has shown that biosimilars are highly similar to their originator product in terms of safety and efficacy. Misconceptions about biosimilars in the dermatology community and concerns around their use in psoriasis were evaluated with a review of the data to clarify their use; the results were presented in 2 posters.

The first poster reviewed the biosimilar approval process to clarify dermatologists' misconceptions about biosimilars. "Dermatologists have approached biosimilar medicines with caution," the researchers wrote.[1]

A recent Cardinal Health report corroborated the sentiment that dermatologists are hesitant to switch to biosimilars. According to the report, only 31% of dermatologists considered themselves very familiar with biosimilars compared with 81% of gastroenterologists, 76% of rheumatologists, and 33% of ophthalmologists.[2]

The authors of the first poster presented at the American Academy of Dermatology (AAD) meeting used a PubMed search to identify studies on the molecular design, preclinical and clinical testing requirements, and approval processes of biosimilars. They described how the complexity of biologics means that even batches of innovator biologics can vary during preclinical testing. "Biosimilars undergo strict preclinical testing and must demonstrate near similarity to the current originator product in quality factors such as receptor binding and pharmacokinetics," the researchers wrote.[1]

Although clinical testing is less stringent for a biosimilar compared with the originator product, the purpose of the clinical testing is to confirm the safety and efficacy of the biosimilar. Then, the use of extrapolation allows for biosimilars to be approved for all indications of the originator product without further testing. As a result, the emphasis of biosimilar product testing is on preclinical rather than clinical testing, the authors noted.[1]

"Physicians who recognize that biologics are too complex to duplicate and who desire indication-specific clinical data on biosimilars might be satisfied knowing biosimilars provide more evidence of similarity than we have for different batches of the innovator product," they concluded. "Regulations that are more stringent for biosimilars than for different batches of innovator products may not be logical."[1]

In the second poster, researchers addressed concerns about the use of biosimilars approved to treat psoriasis using extrapolated evidence from other diseases. They compared efficacy/effectiveness, safety, and drug survival of biosimilars to treat plaque psoriasis with originator products using data from 13 randomized controlled trials (RCTs) and 3 cohort studies. Of the RCTs, 10 were for adalimumab, 2 were for etanercept, and 1 was for infliximab. Of the cohort studies, 1 was for adalimumab, 1 was for etanercept, and 1 was for both etanercept and infliximab.[3]

Eleven trials compared biosimilars with the originator in patients who had never been on the originator product (initiators); 9 trials analyzed switching from the originator product to the biosimilar (switchers). The initiator trials all had similar rates of 75% improvement in the Psoriasis Area and Severity Index and similar adverse events by week 16. The switched trials also had similar outcomes by week 52.[3]

One of the cohort studies reported more adverse events among the group of adalimumab patients switching from the originator to the biosimilar, although the other 2 cohort studies showed no significant differences in safety and effectiveness. "The majority of available evidence suggests similarities between biosimilars and originators," the researchers concluded. "Future pharmacovigilance studies are needed to evaluate the long-term, real-world use of biosimilars for psoriasis treatment."[3]

Adalimumab Biosimilars Available in the US

Biosimilar	Brand
Adalimumab-adbm	Cyltezo
Adalimumab-aqvh	Yusimry
Adalimumab-bwwd	Hadlima
Adalimumab-adaz	Hyrimoz
Adalimumab-fkjp	Hulio

References

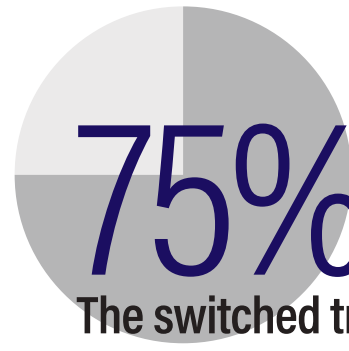
1. Patel P, Purvis C, Hamid R, Feldman S. Biosimilars in dermatology: understanding testing and addressing misconceptions. Presented at: 2023 American Academy of Dermatology Annual Meeting; March 17-21, 2023; New Orleans, LA. Accessed August 21, 2023. https://eposters.aad.org/abstracts/41465

2. 2023 Biosimilars Report. Cardinal Health; 2023. Accessed March 28, 2023. https://www.cardinalhealth.com/content/dam/corp/web/documents/Report/cardinal-health-biosimilars-report-2023.pdf

3. Phan DB, Warren RB, Lunt M, Yiu ZZN. Biosimilars in the treatment of psoriasis – a systematic review of evidence from randomized controlled trials and real-world data. Presented at: 2023 American Academy of Dermatology Annual Meeting; March 17-21, 2023; New Orleans, LA. Accessed August 21, 2023. https://eposters.aad.org/abstracts/42621

11 trials compared biosimilars with the originator in patients who had never been on the originator product (initiators).

9 trials analyzed switching from the originator product to the biosimilar (switchers).



75% PASI improvement in the initiator trials by week 16. The switched trials also had similar outcomes by week 52.

Opzelura®
(ruxolitinib) cream 1.5%

INDICATION

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

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

RELIEF REIMAGINED

#1 PRESCRIBED JAK INHIBITOR IN AD[1]

JAK INHIBITION IN A TOPICAL[2] — IMAGINE THAT.

SCAN HERE TO SEE THE RESULTS.

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, and Medication Guide on the last page.

RAPID REDUCTION OF ITCH & INFLAMMATION[1-5]

>50% OF PATIENTS ACHIEVED CLEAR OR ALMOST CLEAR SKIN (IGA 0/1) with ≥2-point improvement from baseline* at **Week 8** (primary endpoint; 53.8% vs. 15.1% and 51.3% vs. 7.6%; *P* < 0.0001)[2-4]

>50% OF PATIENTS ACHIEVED CLINICALLY MEANINGFUL IMPROVEMENT IN ITCH (NRS4†) at **Week 8** (52.2% vs. 15.4% and 50.7% vs. 16.3%; *P* < 0.0001)[2-4]

DAY 2

DIFFERENCE IN ITCH NRS4 WAS OBSERVED AS EARLY AS DAY 2

POST-HOC, EXPLORATORY ANALYSIS
(NRS ≥ 4; 11.6% vs. 2.9% and 10.8% vs. 1.3%)[1,5]

STUDY DESIGN: 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 pediatric patients ≥12 years of age with an affected BSA of 3% to 20% and an IGA score of 2 to 3 on a severity scale of 0 to 4. Patients were randomized to monotherapy with OPZELURA, ruxolitinib cream 0.75%, or vehicle twice daily for 8 weeks.[2]

*Measured by IGA-TS, defined as the achievement of clear (IGA 0) or almost clear (IGA 1) skin with at least a 2-point improvement from baseline.[2]
†Itch NRS4 is defined as the achievement of at least a 4-point improvement in daily itch on a 0- to 10-point scale, considered a clinically meaningful response; patients in the analysis had an NRS score ≥4 at baseline.[2,3]

AD, atopic dermatitis; BSA, body surface area; IGA, Investigator's Global Assessment; IGA-TS, Investigator's Global Assessment treatment success; NRS, numerical rating scale.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

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

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

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

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

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

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

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

See Important Safety Information continued on the next page.

IMPORTANT SAFETY INFORMATION FOR OPZELURA® (RUXOLITINIB) CREAM 1.5% (CONTINUED)

MORTALITY

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

MALIGNANCIES

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

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

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

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS

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

Thrombocytopenia, Anemia, and Neutropenia

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

Lipid Elevations

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

Adverse Reactions

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

Pregnancy

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

Lactation

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

Please see the Brief Summary of the Full Prescribing Information, including Boxed Warning, and Medication Guide on the next page.

REFERENCES: 1. Data on File. Incyte Corporation. 2023. **2.** OPZELURA [Prescribing information]. Wilmington, DE: Incyte Corporation; 2023. **3.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* 2021;85(4):863-872. doi:10.1016/j.jaad.2021.04.085 **4.** Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol.* 2021;85(suppl):863-872. doi:10.1016/j.jaad.2021.04.085 **5.** Blauvelt A, Kircik L, Papp K, et al. Rapid pruritus reduction with ruxolitinib cream treatment in patients with atopic dermatitis [published online September 6, 2022]. *J Eur Acad Dermatol Venereol.* doi:10.1111/jdv.18571

Incyte Dermatology

MAT-OPZ-01766

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 adult and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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

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

SERIOUS INFECTIONS

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

Reported infections include:

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

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

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

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

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing an oral JAK inhibitor to tumor necrosis factor (TNF) blocker treatment, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Malignancies were reported in patients treated with OPZELURA. Lymphoma and other malignancies have been observed in patients receiving JAK inhibitors used to treat inflammatory conditions. In RA patients treated with an oral JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

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

THROMBOSIS

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

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral Janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of 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: In a large, randomized, postmarketing safety study of an oral JAK inhibitor in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral JAK inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Malignancies, including lymphomas, have occurred in patients receiving JAK inhibitors used to treat inflammatory conditions. In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate. Exposure to sunlight and UV light should be limited by wearing protective clothing and using broad-spectrum sunscreen.

Major Adverse Cardiovascular Events (MACE): In a large, randomized, postmarketing safety study of an oral JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OPZELURA in patients that have experienced a myocardial infarction or stroke.

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

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

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

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (TRuE-AD1 and TRuE-AD2), 499 adult and pediatric subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in TRuE-AD1 and TRuE-AD2 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 is a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

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

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

Data

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

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5-6 elimination half-lives).

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

Pediatric Use: Atopic Dermatitis: The safety and effectiveness of OPZELURA for the topical treatment of mild-to-moderate atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age. Use of OPZELURA in this age group is supported by evidence from TRuE-AD1 and TRuE-AD2, which included 92 pediatric subjects aged 12 to 17 years with mild-to-moderate atopic dermatitis. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age with atopic dermatitis have not been established.

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

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 (9%) were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between subjects less than 65 years and subjects 65 years and older.

PATIENT COUNSELING INFORMATION

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

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

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA. Advise patients that exposure to sunlight, and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions]*.

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

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

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

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

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

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

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

Manufactured for:
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Wilmington, DE 19803

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The Retirement "Red Zone": What You Need to Know to Score Financially

FINANCE & PRACTICE MANAGEMENT with David Mandell, JD, MBA; and Andrew Taylor, CFP

AS FOOTBALL FANS KNOW, the "red zone" is the area of the field where the offense is within 20 yards of scoring a touchdown. Applied to retirement, the red zone concept means the period where retirement is in the near future.

For a financially successful retirement, 3 tactics should be employed during the "retirement red zone" and into retirement itself: developing a budget, reviewing asset allocation, and designing a withdrawal strategy.

Developing a Budget

It may seem like simplistic advice, but budgeting can either push a retirement plan to success or drive it to failure. To begin the budgeting process, physicians should make a list of their lifestyle needs, including necessities such as meals, mortgage, utilities, and insurance, as well as savings contributions.

Deciding how much to save today will depend on how much one expects to spend during retirement. There is no way of determining that without attempting to project future expenses. One can accomplish this by creating budgets based on various postretirement factors including location, size of home, hobbies, frequency of vacations, and other lifestyle expectations. These budget exercises provide a broader view of how effective a retirement savings plan can be based on various lifestyle decisions. It may be helpful to model multiple scenarios, including an aggressive and conservative budget.

A common mistake made by many investors during this exercise is assuming substantial investment returns to justify expensive lifestyle choices. Expecting massive returns on minimal savings is dangerous to a retirement plan. Investors, including dermatologists, should consult with an adviser to determine a reasonable expected return based on historical performance, portfolio components, and other factors.

Reviewing Asset Allocation

Asset allocation encompasses the types of investments within a portfolio, as well as their various underlying industries, risk, and level of market correlation. One of the most important strategies for proper asset allocation is diversification.

Diversification is the process of varying the allocation of value in a portfolio among a variety of sectors, investment types, and risks to reduce each investment's correlation with the others, thus ensuring some buffer against significant swings depleting an entire portfolio. Proper diversification offers one of the most effective ways of mitigating losses.

For investors to understand the importance of diversification, they should realize that history tends to repeat itself, and one unfortunate outcome can result in a complete loss of a lifetime of savings. One example is the employees who were overly invested in Enron stock in the early 2000s. According to *The New York Times*, the Enron 401(k) plan, which was overweighted in Enron shares, lost more than $1 billion in value in 2001 when the company went bankrupt, and shares of Enron stock fell 94%.[1]

Putting Returns in Their Place

Risk tolerance is an investor's ability to mentally and financially withstand volatility in investment performance. An investor with a high risk tolerance may be young, with decades of expected income, and unbothered by large swings in investment values. A more conservative investor may be one with fewer working years through which to replenish certain investment losses.

As physicians age and their investment time horizon shortens, they should consider reallocating their assets into increasingly conservative investments to best limit their exposure to loss. Additionally, careful consideration must be made to properly limit downside risk, potentially through fixed income and alternative investments.

The idea of reallocating to more conservative assets can be troubling to those who are focused on maximizing returns because conservative investments tend to have limited upside potential. To understand why this move is often more beneficial than seeking higher returns in later life, one should be familiar with sequence of returns risk.

Sequence of returns risk is the danger that the timing of liquidation and withdrawal from a retirement account will coincide with a downturn in the market. If it does, then it effectively reduces the overall potential performance of the entire portfolio because a high number of shares will need to be liquidated to get the income expected, thus leaving fewer shares in the portfolio to grow. Sequence of returns risk may not be as important during the wealth accumulation phase, but during the withdrawal phase it is one of the most critical factors in the overall success of a retirement plan.

Strategizing Withdrawals

Although a dermatologist's primary financial focus is to save and accumulate funds for retirement, the design of a withdrawal strategy is equally important to financial health in retirement.

Selecting a Withdrawal Rate

A fundamental pitfall in static retirement plans is setting a withdrawal rate that is fixed over a retirement period. Consider that, for many physicians, the retirement stage of life is likely to last 20 years or more. In that time, investment yields may vary widely and tax rates and personal spending habits could also change. Because of these changing variables, it is essential that flexibility be built into retirement planning. By having flexible planning models and periodically adjusting them based on real-time results, one can expect to follow a model that can endure throughout retirement, regardless of how many years or decades that retirement may last.

Making Room for Taxes

No one knows what tax rates will be upon retirement. This does not mean physicians should ignore tax planning, but they should account for the potential costs of taxes and design a strategy to minimize them. To do this, one must understand how taxes will affect withdrawals and liquidations. Having a plan that considers which withdrawals will trigger ordinary income taxes, which will incur capital gains, and which will realize no tax is essential.

Lastly, dermatologists should understand that delaying distributions from their assets will have the greatest impact on their ability to have a successful retirement. They may have the option of easing into retirement and exploring varying roles within a practice, perhaps transitioning to a consult-only role. This can allow a physician to generate a supplemental income for several years, thus moderating the stress on their portfolios by reducing the rate of withdrawal.

Conclusion

Most dermatologists see a comfortable retirement as a reward for decades of hard work. Do not let the absence of preretirement planning in the "retirement red zone" hinder this goal. While understanding the 3 strategies above is a good start, there is no substitute for working with an experienced adviser in the field who can make analyses and recommendations specific to your situation. The authors welcome your questions.

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She Was Not 18. Could She Give Informed Consent?

LEGAL EAGLE with David J. Goldberg, MD, JD

JANE, AGED 17 YEARS and a very mature adolescent, presents to "Dr Derm" for removal of a facial nevus. Dr Derm discusses the risk/benefit ratio of such an excision. During the discussion, he determines that she is working a full-time job and lives with her boyfriend in her parents' home. She signs a standard consent form. Dr Derm does not realize that she is 17; he did not ask. Ultimately, she is not happy with the scar and wishes to sue her dermatologist. The basis of her lawsuit is that at age 17 years she was not able to provide informed consent. Dr Derm is aware that, generally, a patient must be 18 years or older to provide informed consent. However, he contends that Jane was highly intelligent, articulate, and had a better understanding of the procedure than some patients aged 19 years might have had. Can Jane, as an adolescent, give informed consent?

From a purely practical point of view, most would agree that today's adolescents are maturing more quickly than ever. A girl aged 17 years during the 1940s or 1950s is not a girl aged 16 years in 2023. Many criminal courts are convinced that a juvenile can be tried as an adult. This being the case, can we say that Jane had the right to be treated as an adult and to make her own medical decisions? Was she legally able to sign an informed consent form?

The general rule has been that until one reaches the age of majority (generally 18 years), one cannot lawfully make a final decision as to medical treatment. There are 2 exceptions that are generally recognized. They are the emergency exception and the "emancipated minor" exception.

An emancipated minor includes an adolescent younger than 18 years (in most jurisdictions) who is married and living away from home, as well as a teen living a totally independent life and for whom the parents have abrogated all responsibilities. Some courts, such as in the state of Washington, have considered age, intelligence, maturity, training, experience, economic independence, and freedom from parental control as determining factors. Other states, such as Vermont, have enacted an "emancipation minor law." This law includes 3 general categories: valid marriage, active military duty, and court-ordered emancipation. The law further states that the child must be aged at least 16 years and have lived apart from the parent or guardian for at least 3 months. It is not clear that Jane can give legal consent in Washington. Because she was still living with her parents, she could not do so in Vermont.[1]

There is another way that courts and legislatures have avoided the strict chronologic aged 18 years rule in some cases. This has been through adoption of the concept known as "the mature minor."

The courts have not provided an exact definition of the mature minor. Regardless, mature minor statutes exist in most jurisdictions, permitting underage adolescents the right to consent to treatment of certain specified medical problems such as sexually transmitted diseases, use of contraception, pregnancy, substance abuse, and mental illness. Nevertheless, courts continue to struggle with the wishes of the adolescent and the need for her to show she fits into one of the exceptions to the general rule that one must be aged 18 years before being permitted to give consent to one's own medical treatment.

There has been a common theme among the court cases. How can a minor who is not aged 18 years demonstrate sufficient maturity to the court? A 1955 New York case was among the first to examine this issue. In the case involving Martin Seiferth Jr, the state tried to take custody of a boy aged 14 years from his parents. Custody was sought so that the teen, who had a severe cleft palate condition, could obtain the necessary plastic surgery. The father believed that "mental healing" could take the place of surgery and had convinced his son of such. The judge found that the child was mature and intelligent, stating: "Schooled as he has been for all of his young years in the existence of forces of nature and his fear of surgery upon the human body, I have come to the conclusion that no order should be made at this time compelling the child to submit to surgery. His condition is not emergent and there is no serious threat to his life or health." The boy was therefore allowed to consent to not having the surgery.[2]

Dr Derm will have difficulty showing that Jane is either emancipated or of appropriate maturity. It is unlikely that a court would rule that she could give informed consent.

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

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EQUIPMENT FOR SALE

AD INDEX

PRACTICE FOR SALE

CAREERS—PENNSYLVANIA

The Department of Dermatology at Penn State Health Milton S. Hershey Medical Center is seeking a full-time Dermatologist to join our practice in State College, PA.

Position Highlights:
- Appointment will be at the Assistant or Associate Professor level
- Join a growing and busy academic practice
- Large primary care referral base
- Highly collaborative culture
- Faculty rank commensurate with experience
- Competitive salary and generous benefits

Position Requirements:
- M.D., M.D./Ph.D. or equivalent degree
- BE/BC Dermatology
- A strong commitment to patient care and education Research interests not required

Community:
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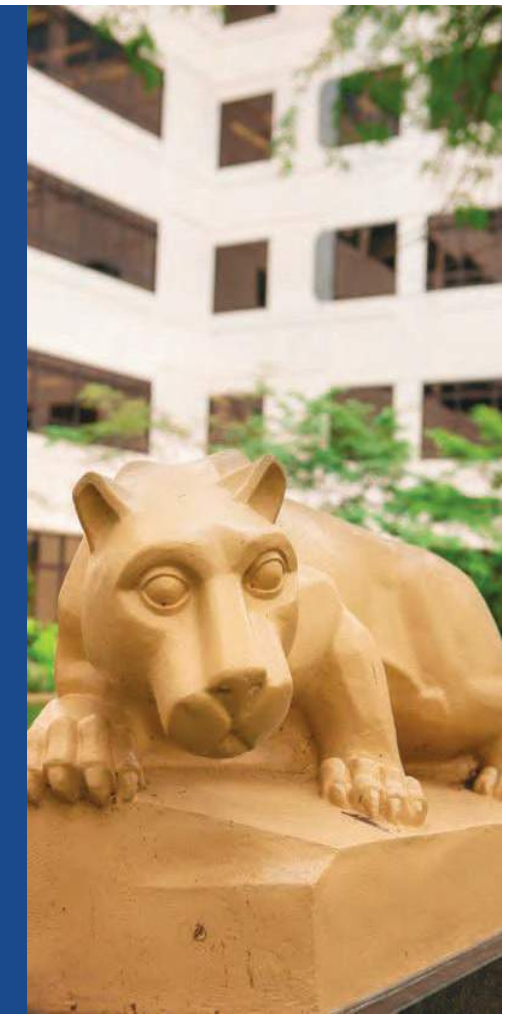

The Department of Dermatology at Penn State Health Milton S. Hershey Medical Center is seeking a full-time Telemedicine Dermatologist to join our practice in Hershey, PA

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- M.D., DO or foreign equivalent
- Completion of accredited training program
- Ability to acquire a license to practice in the State of Pennsylvania
- BC/BE in Dermatology

Position Highlights:
- Appointment will be at the Assistant or Associate Professor level
- Join a growing and busy academic practice
- Large primary care referral base
- Highly collaborative culture
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REFERENCE: 1. Draelos Z, Baalbaki N, Colón G, Dréno B. The effect of ceramide-containing skincare on acne medication induced barrier dysfunction. 30th European Academy of Dermatology and Venereology Congress. 2021.